Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2000-11

Flufenacet

The active ingredient flufenacet and the formulated product Axiom DF for pre-emergent control of specific annual grass and broadleaf weeds in field corn and soybeans, have been granted Section 17 temporary registrations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision concerning these products.

(publié aussi en français)

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Axiom DF, a herbicide developed by Bayer AG for use on field corn and soybeans. Axiom DF herbicide, which contains the active ingredients flufenacet and metribuzin at a ratio of 4:1, is effective against several annual grass and broadleaf weed species common to eastern Canada.

Methods for analyzing flufenacet and metribuzin residues in environmental media are available to research and monitoring agencies upon request to the Pest Management Regulatory Agency.

Bayer AG will be carrying an additional toxicological study as a condition of this temporary registration. Following the review of this new data, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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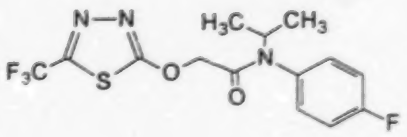
1.0 The active substance, its properties, uses, proposed classification and labelling

1.1 Identity of the active substance and preparation containing it

Active substance:	Flufenacet (formerly fluthiamide, thiafluamide)
Function:	Herbicide
Chemical name: (International Union of Pure and Applied Chemistry):	*N*-(4-Fluorophenyl)-*N*-isopropyl-2-(5-trifluoromethyl-[1,3,4]-thiadiazol-2-yloxy]acetamide
(Chemical Abstracts Service [CAS]):	*N*-4-Fluorophenyl-*N*-(1-methylethyl)-2-{[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy}acetamide
CAS number:	142459-58-3
Nominal purity of active:	95% nominal
Identity of relevant impurities of toxicological, environmental and other significance:	Compounds such as nitrosamines, chlorinated dibenzodioxins, chlorinated dibenzofurans and hexachlorobenzene would not form in this product, given the absence of precursors in the manufacturing process.
Molecular formula:	$C_{14}H_{13}F_4N_3O_2S$
Molecular mass:	363.34
Structural formula:	

1.2 Physical and chemical properties of active substance

Technical product: FOE 5043

Property	Result	Comment
Colour and physical state	Tan solid	
Odour	Pungent, mercaptan-like odour	
Melting point or range	75.5–77.0°C	
Boiling point or range	Not applicable	
Density	1.312 g/mL	
Vapour pressure (for FOE 5043 N-isomer)	Temperature (°C) / Vapour pressure (Pascals [Pa]) 20 / 9×10^{-7} 25 / 2×10^{-6}	Relatively non-volatile
Henry's law constant at 20°C	9×10^{-4} Pa·m^3·mol	Will not volatilize from moist soil and water surfaces
UV and visible spectrum	Depending on the pH, λ_{max} = 206–215 nanometres (nm) Absorption at $\lambda > 350$ nm is not expected	Minimal phototransformation is expected
Solubility in water at 20°C	pH / Solubility (mg/L) 4 / 55.94 7 / 55.91 9 / 53.12	Soluble in water at environmentally relevant pHs, potential for mobility in soil
Solubility (g/L) in organic solvents	Solvent / Solubility (g/L) *n*-hexane / 8.7 toluene / >200 dichloromethane / >200 2-propanol / 170 1-octanol / 88 PEG* / 74 PEG + ethanol / 160 Acetone / >200 DMF / >200 acetonitrile / >200 DMSO / >200	
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 3.2 at 24°C	Potential for bioaccumulation
Dissociation constant	The test substance is not protonated or deprotonated in water	Does not dissociate
Oxidizing properties	Not reduced by zinc metal Oxidized by $KMnO_4$ and $K_2S_2O_8$	
Storage stability	Not applicable to the technical product	

*PEG, polyethylene glycol

End-use product: Axiom DF Herbicide

Property	Result
Colour	Tan to brown colour
Odour	Medicinal odour
Physical state	Granular solid
Formulation type	Water dispersable granule
Guarantee	Flufenacet at 54.4% (nominal) Metribuzin at 13.6% (nominal)
Container material and description	High density polyethylene jug, with a "pinch" handle and a large screw cap closure. The minimum wall thickness of the jug will be at least 0.030–0.050"
Bulk density	32 lb/cu ft (512 kg/cu m)
pH of 1% dispersion in water	3.4
Oxidizing or reducing action	The product does not contain any strong oxidizing or reducing agents
Storage stability	A similar product was claimed to be stable at room temperature, 0, 40 and 50°C for seven weeks in glass containers. The applicant stated that the storage stability study was initiated in January 1998 and a final report will be available in March 1999
Explodability	No explosive potential

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

An isocratic reverse phase (RP) high performance liquid chromatographic (HPLC) method was used for the determination of the active substance and three HPLC methods were used to determine the significant structurally related impurities (content ≥ 0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

An isocratic RP–HPLC method was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy and is suitable for use as an enforcement method.

2.3 Methods for residue analysis

2.3.1 Multiresidue method for residue analysis

The multiresidue method of analysis was not provided for the determination of flufenacet equivalent residues in field corn and soybean.

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) was defined from the corn and soybean metabolism studies as the parent compound, flufenacet, and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

The analytical method involved the conversion of the parent flufenacet and its major metabolites through oxidation and subsequent hydrolysis to a common analyte, 4-fluoro-*N*-methylethyl benzeneamine. Residues of 4-fluoro-*N*-methylethyl benzeneamine were removed from matrices by steam distillation followed by derivatization to the 4-fluoro-*N*-methylethyl benzeneamine trifluoroacetamide for quantification by gas chromatography with mass selective detection (GC–MSD) and were reported as flufenacet equivalent. The limits of quantification (LOQ) were 0.1 parts per million (ppm) for forage, fodder and hay and 0.05 ppm for corn grain and soybean seeds. Recoveries of flufenacet equivalents in corn grain and soybean seeds were 78–104% and 89–114%, respectively. The standard deviations for the recoveries at the spiking level at LOQ indicated good repeatability of the method. Representative chromatograms of control and spiked samples of plant commodities at the LOQ showed no background interferences from the matrix coextractives, good peak shapes, detectability and sensitivity. Good linearity for the method of determination of the residues was observed in the range of 0.025–0.5 ppm with a correlation coefficient, *r*, of 0.999. Analytical method was validated by extracting flufenacet derived residues from the aged radioactive plant matrices collected from the plant metabolism studies. The validation supported the repeatability and reproducibility of the analytical method for the determination of flufenacet equivalent residues in corn and soybean matrices.

2.3.3 Methods for residue analysis of food of animal origin

The ROC was defined from the goat and poultry metabolism studies as the parent compound, flufenacet, and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

The common moiety method (GC–MSD) used to determine residues of flufenacet equivalents containing the 4-fluoro-*N*-methylethyl benzeneamine moiety in plant matrices was also used for the determination of residues in animal matrices. The LOQ for milk was 0.01 ppm and 0.05 ppm for meat and meat by-products. The analytical method was validated by extracting flufenacet derived residues from the aged radioactive goat tissues and milk samples collected from the animal metabolism studies. The validation supported the repeatability and reproducibility of the analytical method for the determination of flufenacet equivalent residues in livestock matrices.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

3.1.1 Absorption, distribution, metabolism and excretion

In a metabolism study in rats flufenacet (98–99.8% active ingredient [a.i.]) was administered to groups of Sprague–Dawley (SD) rats (5–10/sex/dose) using three radiolabels. In the [fluorophenyl-UL-^{14}C] flufenacet experiments, single low (1 mg/kg body weight [bw]), single high (150 mg/kg bw) and multiple low (1 mg/kg bw for 14 days) doses were examined. In the [thiadiazole-2-^{14}C] flufenacet experiments, single low (1 mg/kg bw) and single high (150 mg/kg bw) doses were examined. In the [thiadiazole-5-^{14}C] flufenacet experiments, single low (1 mg/kg bw) and single high (150 mg/kg bw) doses were examined. Flufenacet was rapidly absorbed and metabolized by both sexes following oral exposure to either single or multiple doses. In all experiments, the recovered radioactivity ranged from 93 to 102%, and at least 91% of the administered radiolabel was recovered in the excreta and expired gases within 72 hours (h) post-dose. The urine was the major route of excretion following all dosing regimens, and smaller amounts of radiolabel were eliminated as CO_2 and CH_4 following [thiadiazole-2-^{14}C] flufenacet dosing only. A maximum of 7% of the total recovered radiolabel was found in the tissues and carcass in all experiments. Twenty-five metabolites arising from the fluorophenyl portion of the molecule were detected in the excreta, and 17 of these were positively identified. There were 14 metabolites from the thiadiazole portion of the molecule, and six of these were positively identified. The total amount of radiolabel identified in the various experiments ranged from 67 to 86%, [fluorophenyl-UL-^{14}C] flufenacet; 84 to 92%, [thiadiazole-2-^{14}C] flufenacet; and 53 to 69%, [thiadiazole-5-^{14}C] flufenacet. All unidentified residues in the excreta were characterized.

3.1.2 Acute toxicity: technical and formulation

Technical flufenacet was evaluated in a battery of nine tests. It was slightly toxic in mice, moderately toxic in rats (lethal dose 50% [LD_{50}] = 589 mg/kg bw), was not toxic at the limit dose by dermal application in rats (LD_{50} > 2 g/kg bw) and was of low inhalation toxicity in rats (lethal concentration 50% [LC_{50}] = 3.74 mg/L). It was minimally irritating to the rabbit eye and non-irritating to rabbit skin, and in guinea pigs, it displayed a skin-sensitizing potential.

The formulation Axiom 68DF herbicide has a toxicity profile similar to that of flufenacet technical. This formulation was moderately toxic via the oral route (LD_{50} = 693 mg/kg bw), was of low toxicity by the dermal route (LD_{50} > 2 g/kg bw), was slightly toxic by the inhalation route in rats (LC_{50} = 2.31 mg/L), was minimally irritating to the rabbit eye, was non-irritating to rabbit skin and was a slight skin sensitizer in guinea pigs.

3.1.3 Genotoxicity

Flufenacet was evaluated in a standard battery of five genotoxicity and mutagenicity tests. These included tests for the detection of point mutations (microbial and mammalian microsome mutagenicity assay), the detection of unscheduled deoxyribonucleic acid (DNA) synthesis, the detection of damage to the chromosomes or the mitotic apparatus (in vivo mouse micronucleus test), the detection of base pair mutations, frameshift mutations and small deletions (in vitro gene mutation in V79 cells), and the detection of chromosomal aberrations (in vitro CHO cytogenetic assay). The results of these assays indicated that flufenacet was neither mutagenic nor genotoxic under the test conditions.

3.1.4 Subchronic and chronic toxicity

The subchronic and chronic toxicity of flufenacet were investigated in mice, rats and dogs. A 21-day dermal study was also carried out in rats.

3.1.4.1 Subchronic and chronic toxicity in the mouse

In a 13-week study, flufenacet (93.8% a.i.) was administered to 15 CD-1 [ICR]/BR mice/sex/group for 90 days at a dietary concentration of 0, 100, 400, 1600 and 4000 ppm (equal to 0, 18.2, 64.2, 275 and 824 mg/kg bw/day for males and to 0, 24.5, 91.3, 432 and 1134 mg/kg bw/day in females). The target organs in the study were the liver, thyroid, nervous and hematopoietic systems. There was a dose–response effect in the severity of effects in these organs, with neurotoxicity (circling, increased activity and head swaying) observed only at 1600 ppm and higher. In the liver, effects included hepatocytomegaly (400 ppm and higher) increased absolute and relative weights and individual cell necrosis (1600 ppm and higher). The effects on the thyroid included increased colloid (400 ppm and higher) and decreased thyroxine (T_4) (1600 ppm and higher). Regenerative anemia was indicated by splenic hematopoeisis and pigmentation at 400 ppm and higher along with decreased red blood cell parameters (hemoglobin [Hb], red blood cells [RBC] and hematocrit [Hct]) at 1600 ppm and greater. At the highest dose, ovary weights were decreased.

On the basis of systemic toxicity and histopathology of the liver, spleen and thyroid, the lowest observed effect level (LOEL) is 400 ppm (males, 64.2 mg/kg bw/day and females, 91.3 mg/kg bw/day). The no observed effect level (NOEL) for systemic toxicity was 100 ppm (males, 18.2 mg/kg bw/day and females, 24.5 mg/kg bw/day).

In a mouse carcinogenicity study, flufenacet (technical, 98.2% a.i.) was administered to CD-1 mice (49–50/sex/group) for up to 20 months at dietary levels of 0, 50, 200 or 400 ppm (equal to 0, 7.4, 30.4 or 62.2 mg/kg bw/day in males and 0, 9.4, 38.4 or 77.2 mg/kg bw/day in females). Chronic toxicity was characterized in mice by a dose-related increase, compared with concurrent controls, in (1) ocular effects (observed at necropsy) in males at 50 ppm and in mice of both sexes at 200 and 400 ppm, (2) blood methemoglobin content in mice of both sexes at 200 and 400 ppm, and (3) the histopathological evaluation detected a statistically significant increase in the incidence of cataracts in all dosed males and in females at 200 and 400 ppm. Clinical and cage-side

observations detected an increased incidence of general opacity of the eye in the high-dose mice of both sexes and paleness of the eye in 200 and 400 ppm mice of both sexes. At necropsy, treatment-related opacity of the eyes was detected in the high-dose mice of both sexes. Compared with concurrent controls at the 13- and 18-month intervals, group mean values for blood methemoglobin were increased in the 200 and 400 ppm mice of both sexes, although a dose– response effect was observed in males only at month 13 and in females only at month 18. In the 200 and 400 ppm females at the same intervals, methemoglobin was increased only at the 18-month interval. The sponsor correlated these effects on methemoglobin to the histopathological changes detected in the eyes. It is known that oxidative stress results in oxyhemoglobin-catalyzed glutathione depletion and methemoglobin production. There is strong evidence that glutathione depletion, without methemoglobin production, is also associated with the appearance of cataracts. Indeed in vivo inhibition of glutathione synthesis (with buthionine sulfoximine treatment of rats and mice) leads to the development of cataracts. On the basis of cataract incidence and severity, the chronic LOEL for females was 200 ppm (38.4 mg/kg bw/day) and for males 50 ppm (7.4 mg/kg bw/day) and the NOEL was 50 ppm (9.4 mg/kg bw/day) in females and less than 50 ppm (<7.4 mg/kg bw/day) in males. Under the conditions of this study, there was no evidence of carcinogenic potential.

3.1.4.2 Subchronic and chronic toxicity in the rat

Technical flufenacet (purity 97.0–98.5%) moistened with water was administered topically to intact skin under six-hour occlusive conditions to groups of female and male rats (8/sex/group) at daily doses of 20, 150 or 1000 mg/kg bw/day for at least 22 consecutive days. An additional group of rats (8/sex) served as vehicle (100% water) controls, while other groups of rats (8/sex) in the control and high-dose groups were treated and maintained for two weeks beyond treatment, to gauge the extent of recovery. No treatment-related deaths or dermal irritation were observed. Administration of the test article did not result in any reduction in body weight, body-weight gain, or food consumption. No treatment-related gross lesions were noted in any rat. At the high dose, T_4 and free thyroxine (FT_4) levels were both significantly decreased in both sexes. In addition, FT_4 was significantly decreased in 150 mg/kg bw males, while T_4 was lower but not significantly in the same group. These differences had disappeared after the recovery period. Male liver weights, both absolute and relative, were significantly increased over control values in a dose-related manner in both the 150 and 1000 mg/kg bw/day groups, with normalization to control levels after the recovery period. Centrilobular hepatocytomegaly seen in the high-dose females only cleared after the recovery period. Animals treated with 1000 mg/kg bw/day demonstrated a complete recovery from all treatment responses by two weeks after the final dermal application. In this study, the NOEL for dermal irritation was 1000 mg/kg bw/day and the NOEL for systemic effects was 20 mg/kg bw/day for both sexes.

In a subchronic toxicity study, flufenacet (92.6–94.8% a.i.) was administered to Fischer 344 rats (15/sex/dose) via diet at dose levels of 0, 100, 400, 1600 or 3000 ppm (equal to 0, 6.0, 24.3, 109.1 or 191.2 mg/kg bw/day for males and 0, 7.2, 28.8, 127.2 or 224.5 mg/kg bw/day for females) for 84 days. Body weights and body-weight gains were low compared with controls in males and females treated at 1600 and 3000 ppm.

Flufenacet had significant, dosage-related effects indicative of anemia on the hematology of the treated rats at all treatment levels. Parameters affected were Hb, erythrocyte counts, Hct, reticulocyte and platelet levels. White blood cell levels were noted as being high in males treated at 400 ppm or more. Clinical chemistry parameters that were affected included potassium, cholesterol, alkaline phosphatase (ALP), T_4, tri-iodothyronine (T_3), glucose, triglycerides, uric acid, aspartate aminotransferase (AST), alanine aminotransferase, total protein, albumin, globulin and gamma glutamyl transferase and phosphate. Kidney weights were lower than controls in males and females treated at 1600 ppm or more. Kidneys of male rats in the 400 ppm groups contained variable size hyaline bodies in tubular cell cytoplasm and exhibited hyperplasia of pelvic epithelial cells. Kidneys of female rats contained a brown pigment. Absolute and relative liver weights were high in males and females treated at 1600 ppm or more (males treated at 400 ppm also had high relative liver weights). The cells in the liver of all male and female rats in the 400, 1600 or 3000 ppm treatment groups were swollen, with both cytomegaly and karyomegaly, and exhibited a proliferation of the smooth endoplasmic reticulum. Necrosis of individual cells was also observed. The prevalence and grade of abnormal or necrotic cells increased with increasing treatment rates. Spleen and thyroid weights were high in males treated at 3000 ppm compared with controls (relative weights were high in males treated at 1600 ppm and more and females treated at 3000 ppm). The spleens of male and female rats in the 400, 1600 or 3000 ppm treatment groups were found to have accumulated a brown granular pigment, tentatively identified as hemosiderin. In thyroids, no significant microscopic abnormalities were noted. The observed marginal effects on hematological and clinical chemistry parameters at 100 ppm were not considered adverse. The no observed adverse effect level (NOAEL), therefore, is at the lowest dose level of 100 ppm, equal to 6.0 mg/kg bw/day.

Flufenacet (97.7% a.i.) was administered in the diet to Fischer 344 rats (50/sex/dose) for 104 weeks (satellite groups of 20/sex for the control and high doses and 10/sex for the low and mid doses were sacrificed at one year). The dose levels used were 0, 25, 400 and 800 ppm (equal to 0, 1.2, 19.3 or 39.0 mg/kg bw/day in males and 0, 1.5, 24.4 or 49.8 mg/kg bw/day in females). Flufenacet was not oncogenic. With the exception of a likely toxicologically-related decrease in body weight and body-weight gain at the mid- and high-dose levels of the females, survival, food consumption, feed efficiency and urine analysis were comparable among the groups in both sexes. There was an increase in absolute and relative liver and spleen and relative heart weight in males at 800 ppm. Females at 400 ppm had increased absolute and relative liver weights. Both sexes displayed a dose-related increase in both absolute and relative thyroid weight with statistical significance being attained in the relative weight of mid- and high-dose females and high-dose males. Hematology primarily showed a dose-related statistically significant increase in methemoglobin in both sexes. Gross pathology and histopathology showed that females at terminal sacrifice had a dose-related increase in non-neoplastic uterine cysts. There was a dose-related effect (not statistically significant) on bone marrow granulocytic hyperplasia in both sexes and a statistically significant increase in lung inflammation and granulomatous in the male low-, mid- and high-dose groups. Increased pigmentation of the spleen was observed at the mid- and high-dose groups, in both sexes, at one year and in males at termination. With respect to the liver, both sexes exhibited hepatocytomegaly at the mid- and high-dose levels at both the one- and two-

year sacrifices, and individual cell necrosis was increased in both sexes in the mid- and high-doses at the one-year sacrifice and only in the high-dose males at study termination. There was an increased incidence of epithelial hyperplasia of the renal pelvis at all dose levels, showing a dose–response effect in both sexes and there was, compared with controls, a statistically significant increase in severity and frequency of renal pelvic mineralization at all dose levels in males and in the mid- and high-dose females. Treated females, at all dose levels compared with control, exhibited vascular mineralization of the heart; there was scleral mineralization of the eyes in both sexes (mid- and high-dose groups) and a general, not toxicologically significant, increase in cataracts. The NOEL for systemic toxicity was less than 25 ppm (1.2 mg/kg bw/day), and the LOEL was 25 ppm (1.2 mg/kg bw/day), on the basis of methemoglobinemia and multi-organ effects in the blood, kidney, spleen, heart and uterus.

3.1.4.3 Subchronic toxicity in the dog

In a subchronic toxicity study in dogs, flufenacet (93.8% a.i.) was administered to beagle dogs (4/sex/group) via the diet at dose levels of 0, 50, 200, 800 or 2400 ppm (equal to 0, 1.67, 7.20, 27.21 and 96.91 mg/kg bw/day for males and 0, 1.70, 6.9, 28.0 and 93.23 mg/kg bw/day for females) for 13 weeks. All dogs survived until study termination with no overt signs of toxicity other than soft feces and a thin appearance. At 200 ppm, decreased T_4 and glucose in both sexes and albumin in males and increased globulin in females were observed. Further effects on the thyroid included decreased T_3 at 800 ppm and greater and hypertrophy of the follicular cells at 2400 ppm (females only). Effects on the liver were confined to the highest dose (hepatocytomegaly, increased weight and clinical chemistry). Histopathological changes in the kidney were seen at 800 ppm and greater (e.g., cytoplasmic vacuolization, hyperplasia at 2400 ppm only). At the highest dose (2400 ppm), effects also included decreased body weight and body-weight gain and vacuolization of the cerebral cortex, with no signs of neurotoxicity. The lowest observed adverse effect level (LOAEL) was 200 ppm, equal to 6.90 mg/kg bw/day. The NOAEL was 50 ppm (1.67 mg/kg bw/day).

In a chronic toxicity study in dogs, technical grade flufenacet (95.2–99.0% a.i.) was administered to beagle dogs (4/sex/group) via the diet at dose levels of 0, 40, 800 or 1600 ppm (equal to 0, 1.29, 27.75 or 62.24 mg/kg bw/day in males and 0, 1.14, 26.82 and 58.78 mg/kg bw/day in females) for at least one year. All dogs survived until study termination. Body weight and body-weight gain were decreased at all dose levels in the first 90 days of the study. Treatment-related effects were observed at all doses, with the liver, thyroid, kidney, eye and nervous system being the target organs. Increased methemoglobin was also seen at all doses. Eye effects at 800 ppm and more included vacuolation of the ciliary body epithelium and peripheral optic retina; abnormal physiological nystagmus was observed at the high dose only. In the liver, vacuolization was seen at 40 ppm and more, with increased liver weights and clinical chemistry at 800 ppm and higher and hepatocytomegaly at 1600 ppm. Thyroid hormones were affected starting at 40 ppm (T_4 only) with increased thyroid weights and hypertrophy of follicular cells (males only) at 1600 ppm. Epithelial hyperplasia in the kidney was seen at 40 ppm and higher, with increased kidney weights and pigmentation at 800 ppm and

higher. Neurotoxicity (clinical signs and axonal histopathology) was observed at 40 ppm and higher. The LOAEL was 40 ppm (1.14 mg/kg bw/day).

3.1.5 Reproductive and developmental toxicity

In a two-generation reproduction study with one litter per generation, flufenacet (95.2–99.0% a.i.) was administered to 30 SD rats/sex/dose via the diet at nominal dose levels of 0, 20, 100 or 500 ppm (equal to 0, 1.4, 7.4 or 37.4 mg/kg bw/day for males and 0, 1.5, 8.2 or 41.1 mg/kg bw/day for females). The pre-mating period was 10 weeks for the parental animal (F_0) generation and 12 weeks for the first offspring (F_1) generation. There was a slight decrease in body weight and a decrease in overall (pre-mating days 0–70) body-weight gain in the F_0 generation females during the pre-mating phase. This decreased body weight of the F_0 generation females was sustained throughout gestation and lactation, but body-weight gain was comparable to the control during these two phases. No other body-weight effects were observed, and there was no effect on survival, food consumption or clinical signs at any dose level. The number of estrous cycles and their length were comparable among the groups in both generations, and insemination and gestation lengths were comparable among the groups in both generations. There were no treatment-related effects on the mating index, fertility index or gestation index in either generation, and the birth index was comparable among the groups in both generations. Absolute and relative liver weights were increased in the high-dose dams in both generations and in the F_1 dams at the mid-dose level. Hepatocytomegaly was observed in both sexes at the high-dose level in both generations, in both sexes at the mid-dose level in the F_1 generation, and in F_1 males at the low-dose level. There was an increase in the number of still births and a slight increase in the number and percent deaths between birth and day 0 in the second generation (F_2) pups at the high-dose level. Additionally, there was an increased number and percent of high-dose dams in both generations with a viability index on day 4 less than 100%. There was no adverse effect observed on pup body weight in either generation, and necropsy findings were comparable among the groups in both generations. The NOEL for systemic toxicity was 20 ppm, equal to 1.4 mg/kg bw/day, on the basis of marginally low pre-mating body weight and body-weight gain in F_0 females, increased liver weights and liver to body weight ratios in F_0 and F_1 females, and hepatocytomegaly in F_0 males and females at 100 ppm and greater. The reproductive NOEL was 100 ppm, equal to 7.4 mg/kg bw/day and the LOEL was 500 ppm, equal to 37.4 mg/kg bw/day, on the basis of increased stillbirths and pup death in early lactation for F_2 pups at the high dose of 500 ppm.

Under the conditions of this developmental toxicity study, the administration of flufenacet (97.2% a.i.) to 30 naturally inseminated Crl:CD® (SD) BR female rats/group via gavage at dose levels of 0 (vehicle carboxymethylcellulose sodium), 5, 25 or 125 mg/kg bw/day from days 6 through 15 of gestation resulted in an initial negative body-weight gain during the first three days of dosing (weight loss compared with individual dams' respective body weights pre-dosing), which was considered to be toxicologically significant associated with a concomitant decrease in food consumption. Corrected maternal body weight was comparable among the groups. Comparable pregnancy rates were observed among the groups, and there were no abortions, premature deliveries or dams with 100% intrauterine deaths. All dams had live fetuses at necropsy,

and there were comparable numbers of corpora lutea, implantations and live fetuses among the groups. Fetal body weight was decreased at the high-dose level compared with the concurrent and historical controls. There were no external or visceral anomalies or variations that could be attributed to treatment, and there was no treatment-related increase in visceral malformations. There were several treatment-related skeletal findings (mainly delays in ossification in the skull, vertebrae, sternebrae and appendages) at the high-dose level that exceeded both the concurrent and historical control incidences, and there was a significant increase in the incidence of extra ribs at the high-dose level compared with the concurrent control. There was no evidence of teratogenicity up to the highest dose tested. The maternal LOEL was 125 mg/kg bw/day, on the basis of decreased body-weight gain initially. The maternal NOEL was 25 mg/kg bw/day. The developmental NOEL was 25 mg/kg bw/day, on the basis of marginally low fetal body weight, delayed development (mainly delays in ossification in the skull, vertebrae, sternebrae and appendages) and an increase in the incidence of extra ribs at 125 mg/kg bw/day.

In a developmental toxicity study, flufenacet (98.5% a.i.) was administered to female New Zealand White (NZW) rabbits (20/group) via gavage at a dose level of 0, 5, 25, 125 or 200 mg/kg bw/day from days 6 through 18 of gestation. Flufenacet showed maternal toxicity at doses of 125 and 200 mg/kg bw/day as evident from clinical signs of toxicity (soft stool), reduced body-weight gain during the treatment period and increased histopathological changes in the liver. Findings in the liver at 25, 125 and 200 mg/kg bw/day included hypertrophy, vacuolar changes characterized by a foamy appearance of the cytoplasm and a ground-glass appearance of the cytoplasm. The NOEL for maternal toxicity was 5 mg/kg bw/day and the LOEL was 25 mg/kg bw/day. There were no treatment-related effects on resorptions or fetal mortality. Flufenacet at a dose of 200 mg/kg bw, however, showed an increased incidence of delayed ossification of the skull and enlarged fontanelles of skull bones. In addition, both 125 and 200 mg/kg bw doses showed an increase in skeletal variations, specifically supernumerary ribs and additional presacral vertebrae. No treatment-related external or visceral malformations were observed in any treatment group. There was no evidence of teratogenicity up to the highest dose tested. The NOEL for developmental toxicity was 25 mg/kg bw/day and the LOEL was 125 mg/kg bw/day, on the basis of increased skeletal variations.

3.1.6 Neurotoxicity (acute, delayed and subchronic)

Twelve Fischer 344 (CDF [F-344]/BR) rats/sex/dose were administered a single gavage dose of flufenacet (98.5–98.2%) in 2% Cremophor EL in distilled water. Dose groups were 0, 75, 200 or 450 mg/kg bw for males and 0, 75, 150 or 300 mg/kg bw for females. Detailed clinical signs were recorded daily for both males and females. Body weights, functional observational battery (FOB), motor and locomotor activities and habituation were assessed pre-treatment, approximately three hours after dosing and at 7 and 14 days following dosing. There were 4/12 and 12/12 deaths in the high-dose male and female groups, respectively, before day 7. There were no additional deaths in the animals surviving to day 14. At termination, there were no treatment-related effects on body weight of either sex, nor were there any gross or microscopic lesions in skeletal or neural tissues. On day 0, high-dose males and females displayed lower activity in their home

cages and in "open field" testing; inappropriate sedentary behaviour was seen in the high-dose males and females and in a single low-dose male. Gait disturbances were seen in 1/12 high-dose females and body temperature was elevated in the mid- and high-dose groups of both males and females. Flufenacet-treated male and female animals had motor and locomotor activities that were lower than control at the mid- and high-doses. This effect was most apparent in the first two test intervals of the nine 10-min test intervals per session. The NOAEL for systemic toxicity and acute neurotoxicity was 75 mg/kg bw, on the basis of minimal clinical signs of toxicity at the low dose (males sitting or lying normally in the open field test) and at higher doses, uncoordinated gait (females) and decreased activity (males) that was reversed by post-dosing day 14.

Twelve Fischer 344 (CDF [F-344]/BR) rats/sex/dose were administered flufenacet (98.2%) in the diet at nominal dose levels of 0, 120, 600 or 3000 ppm (equal to 0, 7.3, 38.1 or 219 mg/kg bw/day for males and 0, 8.4, 42.6 or 247 mg/kg bw/day for females, respectively) for 13 weeks. Neurobehavioural evaluations consisting of FOB and motor activity evaluations were conducted one week pre-treatment, and during study weeks 4, 8 and 13. Food consumption was comparable between all groups; body weights and body-weight gains of all 3000 ppm treated rats were significantly and consistently lower than controls, indicating a treatment-related decrease, relative to controls, in feed efficiency. Treatment-related effects on some of the FOB parameters identified in the high-dose animals included lower forelimb grip strength (males), a slight lack of coordination of the righting reflex (males), lower body temperature (females), lower forelimb and hindlimb grip strength and widened hindlimb foot splay (females). Motor and locomotor activity were higher than controls in the high-dose males (week 13) and females (weeks 8 and 13). Detailed examination of the eyes showed no treatment-related effects, and electroencephalography of rats who were awake showed no treatment-related effects on cortical function. There were no treatment-related effects on terminal brain weight. With the exception of axonal swelling in both sexes (mid and high dose) in the cerebellum and spinal cord of treated animals, there were no treatment-related gross or microscopic lesions in the skeletal muscle or neural tissues. The NOEL for neurotoxicity was 120 ppm equal to 7.3 mg/kg bw/day in males and 8.4 mg/kg bw/day in females, on the basis of microscopic lesions detected at 600 and 3000 ppm dose levels.

3.1.7 Mechanistic studies

The objective of the study described below was to test the hypothesis that an indirect non-thyroidal mechanism (possibly, but not necessarily mediated by the liver) may account for the changes seen in flufenacet-exposed male rats.

Ten male CDF (F-344)/BR rats/dose/time were administered flufenacet in the diet at dose levels of 0, 400, 1600 or 3000 ppm (equal to 0, 21.5, 84.3 or 144.9 mg/kg bw/day, respectively) for 3, 6 and 13 weeks. Treated rats showed a dose-related, time-dependent reversible increase in both liver and thyroid weights. Absolute and relative liver weights were statistically greater than control at all dose levels following a 3-, 6- or 13-week exposure. In the thyroid, multifocal compensatory hypertrophy of the follicular epithelium was seen after 3, 6 and 13 weeks of exposure at the high dose. This was associated with higher absolute (at three weeks only) and relative (at 3, 6 and 13 weeks)

thyroid weights at the 1600 and 3000 ppm dose levels, and following the recovery period, the 3000 ppm group continued to show a significantly greater relative thyroid weight. At the high dose, body weights were lower than control following each exposure period, including the four-week recovery period. There was a dose-related decrease in serum T_4 after 3, 6 and 13 weeks of dosing with flufenacet, whereas T_3 plasma levels were only lower than control at 6 and 13 weeks. At the earliest time point assayed (three weeks) only the 1600 and 3000 ppm dosed rats had T_3 levels lower than control. Following a four-week recovery period, the levels of T_4 and T_3 were similar in all groups, including control, demonstrating reversibility of flufenacet effects. Thyroid weight was increased at 3 (absolute and relative), 6 and 13 weeks (relative to bw only) at all dose levels. Following a four-week recovery period, liver weights did not differ from control but relative thyroid weight remained statistically higher at the mid and high dose. Liver histopathology showed a treatment-related reversible diffuse centrilobular hypertrophy, with increased endoplasmic reticulum proliferation. Serum hormone analysis showed lower total and free serum T_4 levels at all doses and sampling times. Both T_3 (decreases) and thyroid stimulating hormone (increases) showed transient, but erratic, dose-associated changes in circulating levels. After the four-week recovery period, all serum values had normalized and were now comparable to control. Analysis of timed blood samples over a five-week period of oral dosing with feed containing both radiolabelled and unlabelled flufenacet at levels of 400, 1000, 1500, 2000, 2500 and 4000 ppm showed that steady-state blood levels were achieved two to three weeks later.

In a comparative hormonal study, normal and thyroidectomized male rats (4–6/dose group, maintained with T_4 and T_3 infusion) were dosed with flufenacet for three weeks at dose levels of 0, 25, 1000 or 3000 ppm. These doses were chosen on the basis of the observed two- to three-week lag time before flufenacet plasma levels stabilized, consistent treatment-related effects on T_4 blood levels and effects noted in the rat chronic study. Weekly blood samples showed that flufenacet caused a similar decrease in total T_4 and FT_4 levels in both the euthyroid and the thyroidectomized (+T_4 and T_3) groups. These findings demonstrated that flufenacet did not interfere with either the synthesis or secretory capabilities of the thyroid, as in the thyroidectomized rats the hormone source was the minipump. In euthyroid rats (6/group) dosed with either 0 or 1000 ppm flufenacet for 21 days, there was no difference observed in the ability of the thyroid glands to sequester iodide, indicating no effect on either iodide transport or storage. These results indicate that flufenacet alterations of serum thyroid hormone levels, most notably T_4, were most likely mediated indirectly, through increased hepatic metabolism, rather than by way of a direct effect on the thyroid gland.

3.1.8 Integrated toxicological summary

Metabolism studies in rats demonstrated that flufenacet was rapidly absorbed, metabolized and excreted by both sexes following oral exposure to either single or multiple doses. In the [fluorophenyl-UL-^{14}C]-labelled flufenacet experiments, the recovered radioactivity ranged from 60 to 75%, and at least 91% of the administered radiolabel was recovered in the experiments with [thiadiazole-2-^{14}C]-labelled flufenacet within 72 h post-dose. The urine was the major route of excretion following all dosing regimens, and for the [fluorophenyl-UL-^{14}C]-labelled flufenacet, smaller amounts of

radiolabel were eliminated as CO_2 and CH_4. No volatile radiolabelled compounds were detected after dosing with [thiadiazole-2-^{14}C]-labelled flufenacet, indicating that the phenyl ring was not cleaved. The analysis of the plasma curves indicated that after dosing with [fluorophenyl-UL-^{14}C]- and [thiadiazole-2-^{14}C]-labelled flufenacet, only the fluorophenyl portion of the molecule was subjected to enterohepatic circulation. Tissue residues were very low, often at the limits of detection, indicating a low propensity for accumulation.

The major metabolites identified in the [fluorophenyl-UL-^{14}C]-labelled flufenacet experiments contained only the "fluorophenyl" moiety of the compound. The thiadiazole ring was cleaved before further metabolism. The major metabolic pathway for [fluorophenyl-UL-^{14}C]-labelled flufenacet in rats appeared to be conjugation with glutathione.

Flufenacet was slightly toxic in mice, moderately toxic in rats, was not toxic at the limit dose by dermal application in rabbits and was of low inhalation toxicity in rats. It was minimally irritating to the rabbit eye and non-irritating to rabbit skin, and it was a dermal sensitizer in guinea pigs.

The formulation Axiom DF herbicide has a toxicity profile similar to that of flufenacet technical. This formulation was moderately toxic via the oral route, of low toxicity by the dermal route, was slightly toxic by the inhalation route in rats, was minimally irritating to the rabbit eye, was non-irritating to the rabbit skin and was a slight skin sensitizer in guinea pigs.

In a standard battery of genotoxicity and mutagenicity tests (point mutation, unscheduled DNA synthesis, chromosomal aberration, sister chromatid exchange) flufenacet-technical demonstrated no mutagenic or genotoxic potential.

Short- and long-term feeding studies revealed similar effects in mice, rats and dogs. In the chronic rat toxicity study, the NOEL was *less than* the low dose. In the chronic-rat study, mild treatment-related effects seen at the low-dose included methemoglobinemia, mineralization in the heart and kidney, pigmentation in the spleen and non-neoplastic uterine cysts. The common treatment-related effects noted in *all three* species were in end points related to the following organs: kidneys, hematologic and spleen, and thyroid. Eye effects noted included cataracts (mice and rats), scleral mineralization (rats) and vacuolization of ciliary body epithelium and cystic vacuolization of the peripheral optic retina (dogs). Also, an increased incidence of axonal swelling was observed in the brain and spinal cord of rats and dogs exposed to high levels of flufenacet.

In the 21-day dermal toxicity study, the NOEL for dermal irritation was 1000 mg/kg bw/day for both sexes and the NOEL for systemic effects was 20 mg/kg bw/day. At higher doses, there were reversible clinical chemistry effects (decreased T_4 and FT_4 levels) in both sexes and reversible histopathological liver findings in the females.

In the oncogenic mouse and rat studies, no treatment-related increases of either benign or malignant neoplasms were noted in any tissues, at any dose level, in either sex of either species.

Clinical signs of flufenacet neurotoxicity were seen in the acute and short-term studies. In acute rodent studies, specific clinical signs that were noted included, at low doses, sitting or lying normally in the open field test, and at higher doses uncoordinated gait and decreased activity (mid-dose males) that was reversed by post-dosing day 14. In the short-term rodent study, treatment-related effects on some of the FOB parameters included lower forelimb grip strength, a slight lack of coordination of the righting reflex, lower body temperature, lower forelimb and hindlimb grip strength and widened hindlimb foot splay (males). In contrast, only head tilt was observed in dogs during the latter part of the one-year treatment period.

In the one-year dog study, the pattern of excretion of the urinary metabolites of flufenacet (thiadone, thiadone–glucuronide and the conjugates of cysteine and mercapturic acid) were nonlinear among the dose groups, indicating saturation or exhaustion of metabolic processes at the mid- and high-dose levels where these changes were observed. No NOAEL could be established for the study. At the lowest dose (1.14 mg/kg bw/day), there were decreases in T_4 and increased methemoglobin in both sexes, increased kidney weight and epithelial hyperplasia in males, liver vacuolization in females and clinical and histopathological evidence in neurotoxicity in both sexes. There was a dose–response effect apparent for these effects, in both incidence and severity.

In the 90-day neurotoxicity rat study, there were compound-related motor and neurobehavioural effects at the high dose that were *not* associated, with the exception of axonal swelling in the cerebellum and spinal cord at the high dose, with any microscopic evidence of neurotoxicity. Additionally, in a 55-day mechanistic study in which dogs were dosed with thiadone (a flufenacet metabolite), swollen axons were identified in the brain and spinal cord, and there was decreased gluthathione reductase in the brain stem and cerebellar regions at the mid and high doses only, supporting the view that limitations in gluthathione interdependent pathways and heightened antioxidant stress resulted in these metabolic lesions in the brain. In addition, toxicokinetic monitoring showed that thiadone or its metabolites were detected in the brain extracts of the mid- and high-dose dogs only. The depletion of glutathione interdependent pathways by as little as 20%[1] allows neurotoxicity to develop in high oxygen demand cells, owing to limited redox cycling and oxidative stress, ultimately resulting in apoptosis or cell death.[2] Collectively, these data indicate that these effects were related to high utilization of tissue glutathione, which resulted in reduced cellular protection to oxidative stress.

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1 Reed, D.J., and Fariss, M.W. 1984. Glutathione depletion and susceptibility. **Pharmacological Reviews, 36**: 25S–33S.

2 Younes, M., and Siegers, C.P. 1981. Mechanistic aspects of enhanced lipid peroxidation following glutathione depletion in vivo. **Chemico-Biological Interactions, 34**: 257–266.

In teratology studies, flufenacet was not teratogenic in either rats or rabbits. The multigeneration rat reproduction study showed that flufenacet did not have any adverse reproductive effects. The number of estrous cycles and their length and insemination and gestation lengths were comparable amongst the groups in both generations. There were no treatment-related effects on the mating index, fertility index or gestation index in either generation, and the live birth index was comparable among the groups in both generations. In the parental generation, there was a slight decrease in body weight during the pre-mating phase that was maintained during the gestation and lactation phases, but body-weight gain was comparable to control. No other body-weight effects were observed, and there was no effect on survival, food consumption or clinical signs at any dose level. There were increased stillbirths and pup deaths in the F_2 litters in early lactation at the high dose.

Mechanistic data indicated that the effects observed in rats on thyroid hormone levels and thyroid gland histopathology were the result of increased T_4 clearance by the liver. The thyroid effects were also observed in the dog and the physiological response of the dog to these changes in thyroid hormone homeostasis more accurately reflects the potential human response.

3.2 Determination of acceptable daily intake

The dog was identified as the most appropriate species, on the basis of changes in the liver, erythrocytes, eyes and nervous system, and clinical findings of decreased T_4, glucose and albumin and increased globulin. The clinical chemistry effects of flufenacet, i.e., decreases in T_4 and FT_4, are considered to be sensitive exposure indicators. The physiological response of the dog, rather than the rat, to these changes in thyroid hormone homeostasis more accurately reflects that of humans. It was also demonstrated (in the dog) that the metabolite "thiadone" caused effects similar to those obtained with its parent, flufenacet.

The LOEL of 40 ppm (1.14 mg/kg bw) obtained in the one-year dog study was considered appropriate for calculating the acceptable daily intake (ADI). Because a NOAEL could not be determined in this study, a 300-fold safety factor (SF) to account for interspecies extrapolation (10×), intraspecies variability (10×) and the absence of a NOEL in the critical study (3×) is required. This provides a margin of exposure (MOE) of 1850× to the NOEL for reproductive effects and neurotoxicity.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{SF}} = \frac{1.14 \text{ mg/kg bw/d}}{300} = 0.004 \text{ mg/kg/day of flufenacet}$$

The maximum acceptable intake for a 60-kg person, calculated according to the formula ADI × 60 kg, is 0.24 mg/day.

3.3 Acute reference dose

The NOAEL from the acute neurotoxicity study in rats is considered the most appropriate for the determination of the acute reference dose (ARfD). The NOAEL is 75 mg/kg bw on the basis of minimal clinical signs of toxicity at this dose (males sitting or lying normally in the open field test) and at higher doses uncoordinated gait (high-dose males) and decreased activity (mid-dose males) that was reversed by post-dosing day 14. At the high dose, mortality was observed.

The ARfD proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{SF}} = \frac{75 \text{ mg/kg bw/d}}{100} = 0.75 \text{ mg/kg/day of flufenacet}$$

3.4 Toxicology end point selection

Flufenacet has been shown to be rapidly and extensively metabolized and excreted in the rat with a low propensity for accumulation following single-dose and repeat-dose oral exposures.

Technical flufenacet was slightly acutely toxic in mice, moderately acutely toxic in rats, was not toxic at the limit dose by a single acute dermal application in rats, and was of low acute inhalation toxicity in rats. It was minimally irritating to the rabbit eye and non-irritating to rabbit skin, and it was a dermal sensitizer in guinea pigs. The formulation Axiom DF herbicide has an acute toxicity profile similar to that of flufenacet technical.

Short-term and long-term feeding studies revealed similar effects in mice, rats and dogs. The common treatment-related effects noted in all three species were in end points related to the following organs: liver, kidneys, hematologic and spleen, and thyroid.

Clinical signs of neurotoxicity were observed in acute and short term studies in rodents and dogs. However, results from further studies in rats and dogs, including a mechanistic study in dogs, indicated that neurotoxicity effects were secondary to high utilization of tissue glutathione in the brain, which resulted in reduced cellular protection to oxidative stress. The NOEL for neurotoxicity was 7.3 mg/kg bw/day.

Flufenacet was not tumorigenic in rats or mice, and was not mutagenic or clastogenic.

Flufenacet was not teratogenic in either rats or rabbits. In the multigeneration rat reproduction study, the reproductive NOEL was 7.4 mg/kg bw/day on the basis of increased stillbirths and pup deaths in early lactation for F_2 pups at the high dose of 37.4 mg/kg bw/day.

On the basis of the above noted observations, the short- to intermediate-term nature of the occupational exposure and the predominantly dermal route of exposure for workers, it was considered appropriate to base the occupational risk assessment on the 21-day rat dermal study. This study was well conducted and the NOEL for systemic effects was

20 mg/kg bw/day. At higher doses, there were reversible clinical chemistry effects (decreased T_4 and FT4 levels) in both sexes and reversible histopathological liver effects in the females.

An MOE of 100 is considered to be protective of all workers.

3.5 Drinking water limit

The drinking water limit is addressed in section 4.2.

3.6 Impact on human health arising from exposure to flufenacet

3.6.1 Operator exposure assessment

Significant post-application exposure is not expected since Axiom is applied pre-emergent and any post-application activities during this time period are performed using mechanical equipment such as planters and tillers.

On the basis of the proposed use pattern of Axiom, mixers and loaders or applicators may be potentially exposed to Axiom. This includes both farmers and custom applicators.

Farmers could treat approximately 55 ha of soybeans and 80 ha of corn in a day using groundboom equipment. These crops could also be treated by custom applicators, who could treat approximately 120 and 140 ha per day of soybeans and corn, respectively. At the maximum application rates, approximately 44 kg a.i./day and 96 kg a.i./day could be mixed, loaded and applied by groundboom to soybean by farmers and custom applicators, respectively. For corn, 64 and 112 kg a.i./day could be handled by farmers and custom applicators, respectively. Exposure resulting from the mixing, loading and application of flufenacet would be short term in farmers and short term to intermediate (i.e., a few days to two or three weeks) in custom applicators.

An in vivo dermal absorption study was not submitted. A dermal absorption value of 30% was derived on the basis of comparisons of results in dermal and oral toxicology studies and taking into consideration physical and chemical properties of flufenacet.

A Pesticide Handlers Exposure Database (PHED) (version 1.1) assessment was conducted to assess the mix, load and application exposure to flufenacet during the handling and application of Axiom DF. The PHED is a database of generic mixer, loader and applicator passive dosimetry data that facilitates the generation of scenario specific exposure estimates. The PHED subsets compared well with the proposed formulation and use patterns. All PHED subsets met the criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. The PHED estimates were based on wearing long-sleeved shirts, long pants and gloves when mixing and loading, and long-sleeved shirts, long pants and no gloves when applying. An additional protection factor was added to account for the protective nature of coveralls during mixing, loading and application. A best-fit statistical measure was used for the exposure.

Exposure estimates are summarized in Table 3.1.

For the risk assessment, the exposure estimates were compared with the 21-day dermal rat study, which had a NOEL of 20 mg/kg bw. The MOEs are summarized in Table 3.1.

Table 3.1 Summary of exposure estimates and resulting margins of exposure for mixers, loaders and applicators

Use	Subpopulation exposed	Total exposure[1] (dermal deposition + inhalation) (μg a.i./kg bw/day)	Margin of exposure[2]
Soybean, groundboom	Mixer, loader and applicator: farmer	73.42	272
	Mixer, loader and applicator: custom	160.18	125
Field corn, groundboom	Mixer, loader and applicator: farmer	106.79	187
	Mixer, loader and applicator: custom	186.88	107

[1] The exposure estimates assume a body weight of 70 kg and that, in a typical day, 55 and 120 ha of soybeans are treated by farmers and custom applicators, respectively, and 80 and 140 ha of corn are treated by farmers and custom applicators, respectively, all at the maximum application rate of 0.80 kg flufenacet/ha.

[2] On the basis of a NOEL of 20 mg/kg bw/day from a 21-day dermal rat study.

Use of this NOEL also provides adequate MOEs for the NOEL for reproductive toxicity (7.4 mg/kg bw/day) and the NOEL for neurotoxicity (7.3 mg/kg bw/day). For the most highly exposed work subpopulation (i.e., custom application to corn), systemic exposure was 59.84 μg/kg bw/day. This yields MOEs greater than 120 for both the reproductive toxicity end point and the neurotoxicity end point.

3.6.2 Bystanders

Given that the application is restricted to agricultural areas, and that the product would be applied using ground equipment only, exposure and risk to bystanders is expected to be negligible.

3.6.3 Post-application exposure

Given that flufenacet is applied pre-emergence, there would not be any significant post-application activities associated with its use in soybeans and corn.

4.0 Residues

4.1 Definition of the residues relevant to maximum residue limits

4.1.1 Definition of the residues in field corn relevant to maximum residue limits

Plant metabolism

In the corn metabolism study, flufenacet (Axiom DF 54.4% a.i., water dispersible granular herbicide, labelled in the fluorophenyl ring) was preplant incorporated into sandy loam soil at 1.37 kg a.i./ha (2.2× good agricultural practices [GAP]). Corn was harvested after 96 days as forage and fresh kernels and 110 days as fodder and dry kernels. The total radioactive residues (TRR) identified were 86% (0.26 ppm) in forage and 80% (0.5 ppm) in fodder, with no single unidentified metabolite exceeding 7% of the TRRs. The TRRs were 71% (0.006 ppm) in fresh kernels and 72% (0.008 ppm) in dry kernels. Due to very low levels of radioactivity at exaggerated rates, further metabolite identification was not possible in the kernels. The major radioactive component identified was flufenacet oxalate, forage 44% of TRRs and fodder 41% of TRRs. The parent compound was not detected in either forage or fodder.

In the soybean metabolism study, flufenacet (Axiom DF 54.4% a.i., water dispersible granular herbicide, labelled in the fluorophenyl and thiadiazole rings) was applied to sandy loam soil at 1.45 kg a.i./ha (2.1× GAP). Mature soybean crops were harvested fresh to obtain forage (42 days), beans (66 days), hay and field dried beans (80 days). Total radioactive residues in fresh harvested forage and beans were 92% (8.5 ppm) and 63% (0.5 ppm), respectively. Levels of TRRs in dry harvest hay and beans were 81% (21.7 ppm) and 47% (1.0 ppm), respectively. All remaining residues were characterized on the basis of their extractability and partitioning characteristics. No single metabolite accounted for more than 7% of the recovered radioactivity. In soybeans, the malonylalanine conjugate was predominant. The parent compound was not detected in any of the soybean matrices. On the basis of the corn and soybean metabolism studies, the ROC was defined as flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

Confined crop rotation studies

In the confined crop rotation study, radiolabelled flufenacet was applied to sandy loam soil once at a rate of 0.96 kg a.i./ha (1.6×). Kale (leaves), turnips (tops and roots) and wheat (grain and straw) were planted as secondary crops at 33, 157 and 361 days after treatment (DAT), respectively. Crops were harvested at maturity. Analyses of soil cores, at application and planting, demonstrated that TRRs in soil decreased by approximately half (44%; 0.26 ppm) after 153 days. No parent compound was found in the rotational crops. The LOQ was 0.05 ppm for all matrices. In the event of crop failure, corn or soybean may be replanted immediately in or on treated soil. Winter wheat may be planted four months after an application of flufenacet (Axiom DF). The residue data corroborated the proposed rotational crop plant-back interval of four months for winter wheat. The confined rotational crop study supported the definition of the ROC, i.e., flufenacet and its

metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety, derived from the plant and animal metabolism studies.

Storage stability
For the freezer storage stability study, control samples of corn and soybean were spiked at 1 ppm with flufenacet and five of its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety and stored at –26°C for 0, 6 and 11 months. The data indicated that residues of flufenacet and its metabolites were stable for at least 11 months in corn and soybean matrices. Plant metabolism and residue samples were analyzed within this time frame.

4.1.2 Definition of the residues in food of animal origin relevant to maximum residue limits

Animal metabolism
In the hen metabolism study, flufenacet (54.4% a.i., fluorophenyl- and thiadiazole-labelled flufenacet) was administered orally to Babcock White Leghorn hens, via gelatin capsules, for three consecutive days at a rate of 5 mg/kg bw/day, which was equivalent to 78 ppm in feed (867× GAP).

For the fluorophenyl-labelled flufenacet, most of the extractable TRRs were found in liver (38%; 1.4 ppm), fat (83%; 0.4 ppm) and muscle (66%; 0.2 ppm). The TRRs in eggs plateaued within three days (0.15 ppm), representing less than 7% of the dose. Unmetabolized flufenacet was found in the fat (55%), muscle (3%) and in day-2 contents of eggs (7%). The major metabolites found in all tissues contained the 4-fluoro-*N*-methylethyl benzeneamine moiety.

For the thiadiazole-labelled flufenacet, the major residue was identified as thiadone in liver (83%; 8.6 ppm), muscle (86%; 1.9 ppm), fat (80%; 1.4 ppm) and eggs (86%; 0.65 ppm). The TRRs in eggs plateaued within three days. The parent flufenacet was identified only in fat tissues (15%; 0.27 ppm) and the glucuronic acid conjugate of thiadone was a minor component in liver (9%; 0.94 ppm). For both labels, the anticipated residue levels in tissues and eggs from hens consuming feed items from crops treated at GAP would be 0.002 ppm or less.

The metabolism of fluorophenyl-labelled flufenacet in poultry appeared to be through the formation of mercapturic acid, resulting in metabolites containing methylsulfinyl and methylsulfonyl produced from further metabolism of the cysteine or mercapturic acid conjugates of flufenacet. The major metabolic pathway for the thiadiazole-labelled flufenacet appeared to involve the cleavage of flufenacet to release thiadone, which was then eliminated as glucuronide.

Additional poultry metabolism studies were conducted to determine the metabolic fate of flufenacet oxalate, since no parent compound was found in the feed items and flufenacet oxalate was identified as a representative plant, water and soil metabolite. Phenyl-labelled flufenacet oxalate was administered orally to laying hens, via gelatin capsules, for three consecutive days at a rate of 5 mg/kg bw/day. The major residue found in the eggs and

tissues was unmetabolized flufenacet oxalate, which accounted for 85–96% of TRRs (day-3 eggs, 0.01 ppm; fat, 0.04 ppm; liver, 0.15 ppm; muscle, 0.03 ppm). Similar results were obtained in the flufenacet oxalate goat metabolism study (77–99% of TRRs was unmetabolized flufenacet oxalate in tissues) and the flufenacet oxalate bioavailability study in rats (excreted unchanged in urine and feces). The residue levels on the basis of the anticipated dietary burden of flufenacet oxalate would be less than 0.001 ppm in all matrices.

In the goat metabolism study, flufenacet (54.4% a.i., fluorophenyl- and thiadiazole-labelled flufenacet), was administered orally, via gelatin capsules, to lactating goats for three consecutive days at a rate of 5.0 mg/kg bw/day, which was equivalent to 167 ppm in feed (301× GAP). For the fluorophenyl-labelled flufenacet, the highest TRRs were in kidney (81%; 3.77 ppm), liver (84%; 3.73 ppm), fat (89%; 0.28 ppm), muscle (89%; 0.26 ppm) and milk (87%; 0.30 ppm). Unmetabolized flufenacet was found in fat (2%) and muscle (2%). Major metabolites identified in tissues contained the 4-fluoro-*N*-methylethyl benzeneamine moiety. The metabolism of fluorophenyl-labelled flufenacet in goat appeared to be conjugation with glutathione, which proceeded to the mercapturic acid pathway resulting in methylsulfonyl-containing metabolites.

For the thiadiazole-labelled flufenacet, the major residue was identified as thiadone, accounting for 84–89% of the TRRs in kidney (8.2 ppm), liver (14.6 ppm), muscle (3.2 ppm) and fat (2.5 ppm) and 45% of the TRRs in day-3 milk samples (0.37 ppm). The glucuronic acid conjugate of thiadone was a minor component in kidney (9%; 1.8 ppm), liver (5%; 0.9 ppm), and milk (12%; 0.07 ppm). For both labels, the anticipated residue levels would be 0.01 ppm (fat), 0.07 ppm (kidney), 0.06 ppm (liver) and 0.01 ppm (muscle). The expected residues in milk would be 0.003 ppm or less. The major metabolic pathway for thiadiazole-labelled flufenacet appeared to involve the cleavage of flufenacet to release thiadone, which was then eliminated as glucuronide.

The goat and hen metabolism studies suggested that flufenacet was extensively metabolized in the body with negligible residues of the parent expected in meat, milk or eggs. On the basis of the similarity of the goat, laying hen and rat metabolic profiles, the ROC was defined as flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

Storage stability

Control samples of goat tissues and milk were spiked with flufenacet at levels of 0.1 ppm and stored at –24°C for approximately 30 months. Residues of flufenacet equivalents were stable at –24°C up to 30 months in goat and poultry tissues, eggs and milk. Residues of flufenacet oxalate were stable in goat tissues and milk for approximately 18 months. Animal metabolism and residue samples were analyzed within these time periods.

Livestock feeding study

A feeding study with flufenacet was not conducted, since no residues of the parent compound above the LOQ were detected in feed commodities from treated crops. Since flufenacet oxalate was a novel plant metabolite, however, Holstein dairy cows were

administered radiolabelled flufenacet oxalate for 29 consecutive days at treatment rates equivalent to 14× (7.8 ppm), 44× (24.7 ppm) and 148× (82.4 ppm) in feed. At the highest feeding level, residues of flufenacet oxalate reached a maximum of 0.63 ppm (kidney), 0.18 ppm (liver), 0.10 ppm (fat), 0.09 ppm (muscle) and less than 0.01 ppm (LOQ) in milk samples. At the maximum anticipated dietary burden of 0.5 ppm, therefore, no residues of flufenacet or flufenacet oxalate were expected in the meat or milk of cattle. The proposed label specified not to graze or feed flufenacet-treated corn to livestock within 60 days of application. In the case of soybean, livestock may not graze or feed flufenacet-treated soybean forage, hay or straw.

Poultry feeding study

A poultry feeding study was not conducted, on the basis of the results obtained from the hen metabolism study and crop field trials. Residues in poultry tissues and eggs, arising from the feeding of commodities grown in soil treated with flufenacet at GAP, were expected to be less than 0.001 ppm. Flufenacet oxalate was rapidly excreted and only small amounts were detected in hen tissues and eggs. Also, no residues of the parent compound was found in any of the matrices from the plant metabolism studies.

4.2 Residues relevant to consumer safety

Supervised residue trials studies

North American field trials were conducted on corn and soybean raw agricultural commodities (RAC) treated with flufenacet (dry flowable formulation; 60% a.i. w/w) with a single pre-plant incorporated or pre-emergent broadcast application at a rate of 1 kg a.i./ha. Corn forage was collected at milk stage (90 days preharvest interval [PHI]); fodder and grain at crop maturity (129 days PHI). The highest residues were detected in corn forage (0.36 ppm), corn fodder (0.15 ppm) and corn grain (<0.05 ppm). Soybean seeds were collected at earliest harvest from all field trials at PHIs of 112–184 days. Samples of soybean green forage and dry hay were collected at 39–108 days PHI. The highest values for flufenacet-derived residues detected in soybean commodities were 9 ppm (dry hay), 1 ppm (green forage) and 0.05 ppm (seed) at their respective PHIs. Since flufenacet equivalent residues were so low in corn grain and soybean seeds with the pre-plant incorporated or pre-emergent mode of application, no aspirated grain fractions were collected for analyses.

Processing study

Processing studies were conducted with corn and soybean grown in soil treated with a single pre-emergent application at an exaggerated rate of 5.3 kg a.i./ha (~5× GAP). Corn grain was collected at the earliest dry harvest (164 days PHI) and processed by both wet and dry milling procedures. Soybean seeds were collected from the field trial (137 days PHI) and processed into meal, hulls and oils. Flufenacet equivalent residues were less than LOQ (0.05 ppm) in all corn matrices (starch, flour, corn meal and oils), 0.5 ppm (soybean seed), 0.4 ppm (soybean meal), 0.33 ppm (soybean hulls), and less than 0.05 ppm (soybean oils). Flufenacet residues, therefore, did not concentrate in any of the corn or soybean processed commodities that simulated commercial processing practices.

Dietary risk assessment

A chronic dietary risk assessment was conducted using the 1994–1996 Continuing Survey of Food Intake for Individuals as part of the Dietary Exposure Evaluation Model (DEEM™) Software. The potential daily intake (PDI) was obtained by multiplying the proposed maximum residue limits (MRL) for corn and soybean products by consumption data, which estimates the amount of these commodities eaten by various population subgroups. Milk, meat and meat by-products were included in the assessment at the LOQ to account for any flufenacet equivalent residues transferred from corn and soybean based feeds through livestock to humans. The PDI utilized up to 30% of the ADI (0.004 mg/kg bw) for children one to six years old. Consequently, the proposed domestic use of flufenacet on field corn and soybeans does not pose an unacceptable dietary (both food and water) risk to any segment of the Canadian population including infants, children and adults.

4.3 Residues relevant to worker safety

The residues relevant to worker safety have been addressed in section 3.6.3.

4.4 Proposed maximum residue limits and compliance with existing maximum residue limits

4.4.1 Compliance with existing maximum residue limits in Canada

Since this active ingredient is a new chemical, there are no existing MRLs in Canada.

4.4.2 Proposed maximum residue limits

On the basis of field trial residue data, it is proposed that MRLs of 0.05 and 0.1 ppm be established for residues of flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety in or on field corn grain and soybean seed, respectively. The proposed label indicated that soybean forage, hay or straw should not be grazed (or fed) by livestock. Data from the dairy cattle and poultry feeding studies suggested that the transfer of residues of flufenacet and its 4-fluoro-*N*-methylethyl benzeneamine moiety in milk, meat and meat by-products and eggs resulting from the feeding of field corn treated with flufenacet at GAP were not expected to exceed their respective LOQs. Consequently, an MRL of 0.01 ppm (milk) and 0.05 ppm (meat and meat by-products and eggs) should be established to cover residues of flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety in milk, meat and meat by-products of cattle and poultry and eggs.

4.5 Proposed import tolerances

The proposed MRLs for the domestic use of flufenacet in or on field corn grain and soybean seed are the same as the U.S. tolerances. The United States, however, has not established tolerances in meat, milk or eggs, with the expectation that the anticipated residues would not be detectable.

4.6 Basis for differences, if any, in established or proposed maximum residue limits

The Codex Alimentarius Commission (Food and Agriculture Organization, United Nations) has not established MRLs for residues of flufenacet in or on plant or animal commodities.

5.0 Fate and behaviour in the environment

The fate and behaviour of flufenacet in soil and water was assessed by studying its transformation (through hydrolysis, photolysis and biotransformation) and mobility.

Hydrolysis and photolysis
Flufenacet was stable to hydrolysis at pH 5, 7 and 9. There was no phototransformation of flufenacet on soil (sandy loam soil from Howe, Indiana with 6.2 mg a.i./kg soil), when exposed to a xenon lamp for 30 days at 25 ± 1 °C. Flufenacet was also found to be stable to phototransformation in aqueous solutions, when subjected to continuous irradiation using a xenon lamp for 246 h at 25 ± 1 °C. Hydrolysis and photolysis, therefore, will not be principal routes of flufenacet transformation in the environment.

Aerobic biotransformation in soil
Flufenacet was slightly persistent under aerobic conditions in soil with a dissipation time (50%) (DT_{50}) of 23–39 days. Aerobic biotransformation of flufenacet was studied at 1–2 mg a.i./kg soil for 120 days in three soils from Germany (one loamy sand and two silt loam) at 20 ± 1 °C and 40% of the water holding capacity moisture. At study termination, 3–10% of the applied was present as flufenacet and 12–42% was evolved as CO_2. About 37–58% of the applied ^{14}C was in the form of bound residues at the end of the study. The major transformation product detected was FOE sulfonic acid at 14–23% of the applied ^{14}C at study termination. FOE oxalate was formed as a major transient transformation product at 10–16% of the applied between 14 and 56 days. Other minor transformation products were FOE thioglycolate sulfoxide, FOE methyl sulfoxide, FOE methyl sulfone and thiadone. Aerobic biotransformation is the principal route of transformation of flufenacet in aerobic soil.

Mobility in soil
The adsorption and desorption studies indicated that the potential mobility of flufenacet will be high in loam and silt loam soils. The Freundlich (K_d) and the organic carbon (K_{oc}) adsorption coefficient values were 4–5 mL/g soil and 113–144 mL/g C, respectively. The percentage of the applied amount adsorbed in soils ranged from 37 to 54%. The percentage of adsorbed amount desorbed in soils ranged from 90 to 96%. The adsorption and desorption of FOE sulfonic acid, FOE methyl sulfoxide, FOE oxalate, FOE alcohol and thiadone (transformation products of flufenacet) in four soils from the United States (sandy soil, sandy loam, silty clay loam and silty clay soil) indicated that the mobility of transformation products is moderate to very high in these soils.

The leaching behaviour of ^{14}C-FOE 5043 and its transformation products (FOE sulfonic acid, FOE oxalate, FOE thioglycolate sulfoxide, FOE methyl sulfoxide and FOE

methylsulfone) was studied in 60-cm columns (5 cm internal diameter) of four U.S. soils (Howe, sandy loam; Vero Beach, sand; Stanley, silty loam; and Hagerstown, clay loam) using aged Howe soil. The Howe soil was treated with 8.5 mg a.i./kg soil and aged for 30 days. This aged soil was applied to the top of the soil columns and leached with 1 L of 0.01 weight $CaCl_2$. The leaching period was 96 h for all soils (except the silty loam, which was 504 h) at a flow rate of 10.4 mL/h. At the end of leaching, 22–28% of the applied radioactivity was found in all column leachates, except with the sandy soil (49%). All of the transformation products were detected in leachates from all soils. Concentrations of FOE 5043 in the leachate were 4%, 26% and 1% of the applied ^{14}C in sandy loam, sandy and silty loam soils, respectively. These findings are in good agreement with the results of the adsorption and desorption studies and indicate a leaching potential of the flufenacet and its transformation products.

Terrestrial field dissipation

Field dissipation of flufenacet was studied using FOE 5043 DF (61.3% flufenacet) applied at 1.11 kg a.i./ha. Two bare plot field studies were conducted at Branchton (silt loam) and Simcoe (loam) in Ontario. Soil samples were taken at time intervals from the 0–122 cm soil depth. Flufenacet was moderately persistent in silt loam soil with a half-life of 67 days. Flufenacet was slightly persistent in loam soil with a half-life of 15 days. In another field study at Veron, Wisconsin (loamy sand), FOE 5043 DF was applied at 1.11 kg a.i./ha after six days of corn planting. Flufenacet was slightly persistent under the Wisconsin conditions with a half-life of 29 days. In all these studies, flufenacet was detected primarily in the 0–15 cm soil depth and no transformation products were detected in any of the soil depths sampled. These results are contrary to indications from laboratory biotransformation and mobility studies, as no transformation products were detected, and much less mobility of flufenacet and transformation products was demonstrated under field conditions.

Aerobic and anaerobic biotransformation in aquatics

The aerobic aquatic transformation of ^{14}C-flufenacet at 1.3 mg a.i./L was studied in pond water collected from Branchton, Ontario for 365 days in darkness at 25 ± 1 °C. Transformation of flufenacet started 60 days after study initiation. At the end of the study, 57% of the applied was recovered as flufenacet, 24% as FOE oxalate and only 3% was evolved as CO_2. The minor transformation products identified were FOE alcohol and FOE sulfonic acid. FOE 5043 was persistent in aerobic water with a first-order half life of 458 days. The anaerobic biotransformation of ^{14}C-FOE 5043 was studied at 1 mg a.i./kg soil for 371 days in pond water and soil systems collected from Howe, Indiana at 21 ± 1 °C. FOE 5043 was applied to a previously anaerobic system. FOE 5043 continuously, but slowly, partitioned into the sediment fraction from the water phase. After 91 days of incubation, 77 and 24% of applied amount was present in the water and sediment, respectively (mostly as parent). No major transformation products were identified. The minor transformation products identified were FOE amine acetate, thiadone and thiadone acetate. The amount of CO_2 evolved was only 0.1% of the applied at the end of 91 days. FOE 5043 was persistent in the anaerobic system with a first-order half-life of 542 days. These studies indicate that biotransformation is not a principal route of transformation of flufenacet in aquatic systems under aerobic and anaerobic conditions.

Expected environmental concentration in soil and water

The expected environmental concentrations (EEC) of flufenacet in soil (15 cm depth and 1.5 g/cm^3 bulk density) and water (direct overspray from 30 cm depth), on the basis of the maximum application rate of 800 g a.i./ha, are 0.36 mg a.i./kg soil and 0.27 mg a.i./L, respectively. The EEC of flufenacet in pond water from runoff (on the basis of a one-hectare pond, 30 cm water depth, 100-ha watershed area and exposure of soil to 100% of the applied product) is 0.13 mg a.i./L near soybean and corn fields. The EEC for human drinking water from runoff (on the basis of a 4000 m^3 farm dugout, a watershed of 500 ha, exposure of the soil to 100% of the applied product and 0.5% runoff from soil) is 0.5 mg a.i./L near a soybean and corn field.

6.0 Effects on non-target species: environmental toxicity and risk

6.1 Terrestrial non-target species

Wild birds

Flufenacet is practically non-toxic to mallards on an acute oral and dietary basis. It is slightly toxic to bobwhite quail on an acute oral basis and practically non-toxic on an acute dietary basis (Appendix II). The sublethal effects of flufenacet in bobwhite quail are lower hatchling weight and lower 14-day-old survivor weight. The toxicity symptoms in mallard included decreased female body weight, abnormal ovaries and testes, reduced number of viable embryos, reduced number of eggs laid, reduced number of normal hatchlings, lower hatchling weight and lower number of 14-day-old survivors. On the basis of the daily intake and the LD_{50}, bobwhite quail will need 183 days of feeding to attain a dose equivalent to the LD_{50} of the laboratory population and 14 days to attain a dose equivalent to the no observed effect concentration (NOEC). The corresponding values for mallards are 1770 days and 14 days. These results indicate that the application of flufenacet at the maximum label rate will not have an acute oral effect on bobwhite quail and mallards. Also, there is no potential dietary and chronic (reproductive) risk to bobwhite quail and mallards from Axiom DF application at the proposed rates.

Wild mammals

The effects of flufenacet on wild mammals were extrapolated from the review of laboratory mammalian studies by the Health Evaluation Division. Acute dermal and inhalation toxicity of flufenacet in rat was low. It was found to be a skin sensitizer in guinea pigs. On the basis of the daily intake and the LD_{50}, it will take a rat eight continuous days of feeding to attain a dose equivalent to that of the LD_{50} of the laboratory population (Appendix II). The corresponding value in mice is 18 days. Flufenacet, therefore, does not present an acute risk to rat and mice. The 90-day dietary toxicity studies indicate that there is a potential dietary risk to rat and mice from the application of flufenacet at the proposed application rate, only if they consume contaminated food continuously for 90 days.

Honeybees and earthworms
Flufenacet is relatively non-toxic to honeybees. As the end-use product is applied to soil in the early season before bees become active, flufenacet will not be a risk to the honeybees when applied at the proposed label rates. At the proposed use rates, earthworms are also not at risk (Appendix II).

Non-target terrestrial plants
Flufenacet did not affect the seed germination in the dicot and monocot plants studied (cotton, cucumber, soybean, sunflower, tomato, turnip, corn, onion, wheat and sorghum). In the vegetative vigour test, phytotoxicity symptoms (stunting, leaf distortion and necrosis) were observed in all crop species tested. The most sensitive dicot is tomato and the most sensitive monocot is sorghum. On the basis of the effect concentration (25%) (EC_{25}) data, there is a potential risk to non-target terrestrial plants from the application of flufenacet at the proposed label rate (Appendix II). Mitigative measures, therefore, are needed to protect non-target terrestrial plants.

6.2 Aquatic non-target species

Bioconcentration in fish
The K_{ow} coefficient for flufenacet (3.2) indicates that the flufenacet has a potential for bioaccumulation. FOE 5043 accumulated very rapidly in bluegill sunfish with a total residue bioconcentration factor (uptake rate constant) of 165 for whole fish, 38 for fillet and 103 for viscera. The depuration of flufenacet was rapid. More than 94% of the radioactivity was eliminated from the body at the end of the depuration phase. On the basis of the rapid depuration, bioaccumulation and bioconcentration of flufenacet in fish are not concerns.

Fish
Flufenacet is moderately toxic to cold water, warm water and marine fish. The toxicity symptoms of flufenacet in rainbow trout were darkened colouration, lying on the bottom of the aquaria, laboured respiration, loss of equilibria, lethargy and quiescence. In bluegill sunfish, the sublethal effects were loss of equilibrium, laboured respiration, lying on the bottom and quiescence. The early life stages of fish are more sensitive to flufenacet than the adults (Appendix II). Adult fish were not at risk from the proposed application rates of Axiom DF. The most sensitive end point in the early life-cycle study was for swim up (the developmental stage at which the newly hatched fry begin swimming up from the bottom of the test chamber) in rainbow trout with a NOEC lower than the EEC in water (0.27 mg a.i./L). Application of Axiom DF at the proposed rates, therefore, will pose a risk to the early life stages of the fish. Consequently, mitigative measures are needed to protect juvenile fish.

Aquatic invertebrates
The sublethal effects of flufenacet in *Daphnia magna* were lying at the bottom of the vessel or decreased mobility. The most sensitive end point was the time to first brood and the number of neonates produced per reproductive day. Sublethal effects of flufenacet in mysids were loss of equilibrium and lethargy. On the basis of the most sensitive end point

(LC_{50} of *Hyalella azteca*), there is no potential risk to the aquatic invertebrates at the proposed Axiom DF use rates (Appendix II).

Algae and aquatic vascular plants
On the basis of the most sensitive end points, application of flufenacet at the proposed application rate will pose a risk to algae and aquatic vascular plants (Appendix II). Mitigative measures are needed, therefore, to protect aquatic plants.

6.3 Environmental risk mitigation

On the basis of the data submitted, an assessment of the environmental risks associated with the use of Axiom DF has identified the following concerns:

- Flufenacet is persistent in aquatic systems.
- Flufenacet and its transformation products have a potential to leach in sandy or coarse textured soils.
- Application of Axiom DF at the proposed label rate will pose a potential risk to non-target terrestrial plants.
- Application of Axiom DF at the proposed label rate will pose a potential risk to juvenile fish, algae and aquatic vascular plants.

To protect sensitive non-target terrestrial plants and aquatic organisms, buffer zones of 24 and 40 m, respectively, are required.

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended uses

Axiom DF may be used for pre-emergent application on conventionally tilled field corn (excluding sweet, seed and popcorn) and soybeans in eastern Canada for control of specific annual grass and broadleaf weeds. Axiom DF is effective in controlling green foxtail, yellow foxtail, giant foxtail, barnyard grass and redroot pigweed, and suppressing lamb's-quarters and common ragweed.

Insufficient data for review purposes was submitted to support pre-plant surface, pre-plant incorporated and post-emergent (corn only) application timings, and use in no-tillage systems. Insufficient data was also submitted to support claims of fall panicum, large crabgrass and wild mustard control.

Axiom DF may be applied in tankmix combination with several herbicides for broader spectrum weed control. In field corn, Axiom DF may be tankmixed with Aatrex Nine-0, Banvel and Marksman. In soybeans, Axiom DF may be tankmixed with Sencor 75DF, Lorox DF and Sencor 75DF plus Lorox DF. Rate structures are dependent upon soil texture (Appendix III, Table 1).

Insufficient data for review purposes was submitted to support use on soybeans when applied in a tank mixture with Pursuit Herbicide.

Applications of Axiom DF alone or in tankmix combination are not to be made to sandy soils or coarse textured soils with less than 2% organic matter (OM). In the event of crop failure, only field corn and soybeans may be replanted immediately. Winter wheat may be planted four months after application and any crop the year following product use.

7.1.2 Mode of action

Axiom DF is a co-formulation of flufenacet and metribuzin in a 4:1 ratio. Flufenacet is a chloroacetamide that exhibits a strong effect on meristematic tissue, interferes with membrane function and alters the permeability characteristics of cell membranes. Most susceptible species fail to emerge. Those grasses that do emerge appear twisted, with malformed leaves tightly rolled in the whorl and unable to unroll naturally. Metribuzin is a triazinone, which inhibits photosynthesis at photosystem II Site A. Susceptible species emerge through treated soil but become chlorotic and completely necrotic in sunlight.

Differential tolerance to flufenacet appears to be due to the rate at which flufenacet is metabolized, with rapid metabolism attributed to the lack of injury exhibited by field corn and soybeans. Tolerance to metribuzin appears to be due to the method of metabolism and the rate of deamination.

7.1.3 Crops

Field corn and soybeans are the crops for which data is presented and a label claim is made.

7.1.4 Effectiveness against pests

Efficacy of a pre-emergent application of Axiom DF applied alone and tankmixed with Aatrex Nine-O, Banvel, Marksman, Sencor 75DF, Lorox DF and Sencor 75DF + Lorox DF was studied in a total of 28 conventionally tilled field corn and 34 conventionally tilled soybean trials. Trials were conducted over the four-year period of 1995–1998 at locations in Quebec and Ontario.

Axiom DF applied alone was evaluated for control of green foxtail, yellow foxtail, giant foxtail, barnyard grass, redroot pigweed, common ragweed and common lamb's-quarters within each crop. Control ratings for Axiom DF alone in corn and soybeans were pooled, owing to little difference in mean reported control between crops. The tank mixtures were examined to ensure control of these weeds was not compromised when the tankmix partners were included with Axiom DF. A summary of accepted weed claims follow.

7.1.4.1 Effectiveness against green foxtail (*Setaria viridis*)

Axiom DF alone

Control of green foxtail was reported in 10 field corn and 12 soybean trials conducted over four years at one Quebec and 10 Ontario locations. Four trials were conducted on coarse, 11 on medium and seven on fine textured soils at rates proposed for each. At the minimum rate proposed for each soil type, mean reported control was 95% (number of trials [*n*] = 15) at 33–111 DAT. Across all rates proposed for each soil type, mean reported control was 98% (*n* = 38).

Axiom DF + Aatrex Nine-0

Six side-by-side field corn trials conducted at four locations over two years reported green foxtail control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 94.2% and for the tank mixture was 96.2% (*n* = 6) at 33–111 DAT.

Axiom DF + Banvel

Green foxtail control with Axiom DF alone and in a tank mixture with Banvel at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in seven side-by-side field corn trials conducted at four locations over two years. Mean control with Axiom DF alone was 93.7% and for the tank mixture was 94.0% (*n* = 8) at 31–111 DAT.

Axiom DF + Marksman

Control of green foxtail was reported in six side-by-side field corn trials conducted at four locations over two years that included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 93.7% and for the tank mixture was 98.2% (*n* = 6) at 33–111 DAT.

Axiom DF + Sencor 75DF

Nine side-by-side soybean trials conducted at seven locations over two years reported green foxtail control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a proposed rate. Mean control for Axiom DF alone was 96.0% and for the tank mixture was 89.8% (*n* = 9) at 28–128 DAT.

Axiom DF + Lorox DF

Green foxtail control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in eight side-by-side soybean trials conducted at seven locations over two years. Mean control with Axiom DF alone was 95.8% and for the tank mixture was 94.5% (*n* = 8) at 28–128 DAT.

Axiom DF + Sencor 75DF + Lorox DF
Control of green foxtail was reported in eight side-by-side soybean trials conducted at seven locations over two years that included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 95.8% and for the tank mixture was 93.6% ($n = 6$) at 33–111 DAT.

The data for Axiom DF alone support a claim of green foxtail control. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.2 Effectiveness against yellow foxtail (*Setaria glauca*)

Axiom DF alone
Control of yellow foxtail on medium and fine textured soils was reported in three conventionally tilled field corn and four soybean trials conducted over three years at four Ontario and two Quebec locations. An additional nine trials in which a pre-emergent application was made to no-till field corn (four trials) and soybeans (five trials) over three years at four Ontario locations was also available. Eight trials were conducted on medium, and another eight on fine textured soils at rates proposed for each. At the minimum rate proposed for each soil type, mean reported control was 91.0% ($n = 14$) at 19–102 DAT. Across all rates proposed for each soil type, mean reported control was 92.7% ($n = 33$).

Axiom DF + Aatrex Nine-0
Two conventionally tilled and four no-till field corn trials conducted on medium and fine textured soils at five locations over two years reported yellow foxtail control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 90.3% and for the tank mixture was 92.7% ($n = 6$) at 32–102 DAT.

Axiom DF + Banvel
Yellow foxtail control with Axiom DF alone and in a tank mixture with Banvel at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in two conventionally tilled and four no-till field corn trials conducted on medium and fine textured soils at five locations over two years. Mean control with Axiom DF alone was 90.3% and for the tank mixture was 91.5% ($n = 6$) at 32–102 DAT.

Axiom DF + Marksman
Control of yellow foxtail was reported in two conventionally tilled and two no-till field corn trials conducted on medium and fine textured soils at four locations over two years. Trials included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 95.3% and for the tank mixture was 92.8% ($n = 4$) at 55–102 DAT.

Axiom DF + Sencor 75DF
Two conventionally tilled and four no-till soybean trials conducted at four locations over two years on medium and fine textured soils reported yellow foxtail control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a proposed rate. Mean control for Axiom DF alone was 89.5% and for the tank mixture was 96.5% ($n = 6$) at 19–65 DAT.

Axiom DF + Lorox DF
Yellow foxtail control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported for two conventionally tilled and two no-till soybean trials conducted on medium and fine textured soils at four locations over two years. Mean control with Axiom DF alone was 88.5% and for the tank mixture was 92.0% ($n = 4$) at 19–65 DAT.

Axiom DF + Sencor 75DF + Lorox DF
Control of yellow foxtail was reported in two conventionally tilled and two no-tilled soybean trials conducted on medium and fine textured soils at four locations over two years. Trials included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 88.5% and for the tank mixture was 91.5% ($n = 4$) at 19–65 DAT.

The data for Axiom DF alone support a claim of yellow foxtail control on medium and fine textured soils. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.3 Effectiveness against giant foxtail (*Setaria faberi*)

Axiom DF alone
Control of giant foxtail was reported in five conventionally tilled field corn and three soybean trials conducted over two years at one Quebec and three Ontario locations. Two additional trials in which a pre-emergent application was made to no-till field corn (one trial) and soybeans (one trial) in one year at one location each in Ontario and Quebec were also available. Three trials were conducted on coarse, three on medium and four on fine textured soils at rates proposed for each. At the minimum rate proposed for each soil type, mean reported control was 95.7% ($n = 6$) at 47–126 DAT. Across all rates proposed for each soil type, mean reported control was 95.6% ($n = 17$).

Axiom DF + Aatrex Nine-0
Five conventionally tilled and one no-till field corn trials conducted at five locations over two years reported giant foxtail control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 96.5% and for the tank mixture was 96.8% ($n = 6$) at 42–111 DAT.

Axiom DF + Banvel
Giant foxtail control with Axiom DF alone and in a tank mixture with Banvel at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in five conventionally tilled and one no-till field corn trials conducted at five locations over two years. Mean control with Axiom DF alone was 96.5% and for the tank mixture was 95.2% ($n = 6$) at 42–111 DAT.

Axiom DF + Marksman
Control of giant foxtail was reported in five conventionally tilled and one no-till field corn trials conducted at five locations over two years, which included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 96.5% and for the tank mixture was 98.2% ($n = 6$) at 42–111 DAT.

Axiom DF + Sencor 75DF
Two conventionally tilled trials conducted at two locations over two years reported giant foxtail control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a proposed rate. Mean control for Axiom DF alone was 92.0% and for the tank mixture was 98.5% ($n = 2$) at 78–126 DAT.

Axiom DF + Lorox DF
Giant foxtail control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in two conventionally tilled soybean trials conducted at two locations over two years. Mean control with Axiom DF alone was 92.0% and for the tank mixture was 97.0% ($n = 2$) at 78–126 DAT.

Axiom DF + Sencor 75DF + Lorox DF
Control of giant foxtail was reported in two conventionally tilled soybean trials conducted at two locations over two years, which included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 92.0% and for the tank mixture was 98.5% ($n = 2$) at 78–126 DAT.

The data for Axiom DF alone support a claim of giant foxtail control. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.4 Effectiveness against barnyard grass (*Echinochloa crusgalli*)

Axiom DF alone
Control of barnyard grass on medium and fine textured soils was reported in three conventionally tilled field corn and seven soybean trials conducted over three years at one Quebec and five Ontario locations. An additional five trials in which a pre-emergent application was made to no-till field corn (two trials) and soybeans (three trials) over two years at two Ontario locations was also available. Seven trials were conducted on medium, and eight on fine textured soils at rates proposed for each. At the minimum rate

proposed for each soil type, mean reported control was 89.1% (n = 12) at 27–89 DAT. Across all rates proposed for each soil type, mean reported control was 90.5% (n = 31).

Axiom DF + Aatrex Nine-0

Two conventionally tilled and two no-till field corn trials conducted on medium and fine textured soils at three locations over two years reported barnyard grass control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 74.0% and for the tank mixture was 79.5% (n = 4) at 32–89 DAT.

Axiom DF + Banvel

Barnyard grass control with Axiom DF alone and in a tank mixture with Banvel at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in two conventionally tilled and two no-till field corn trials conducted on medium and fine textured soils at three locations over two years. Mean control with Axiom DF alone was 74.0% and for the tank mixture was 83.3% (n = 4) at 32–89 DAT.

Axiom DF + Marksman

Control of barnyard grass was reported in two conventionally tilled field corn trials conducted on medium and fine textured soils at two locations in one year. Trials included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 68.0% and for the tank mixture was 81.0% (n = 2) at 58–89 DAT.

Axiom DF + Sencor 75DF

Three conventionally tilled and three no-till soybean trials conducted at five locations over two years on medium and fine textured soils reported barnyard grass control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a proposed rate. Mean control for Axiom DF alone was 92.2% and for the tank mixture was 93.3% (n = 6) at 35–65 DAT.

Axiom DF + Lorox DF

Barnyard grass control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in three conventionally tilled and one no-till soybean trials conducted on medium and fine textured soils at four locations over two years. Mean control with Axiom DF alone was 92.3% and for the tank mixture was 92.8% (n = 4) at 35–65 DAT.

Axiom DF + Sencor 75DF + Lorox DF

Control of barnyard grass was reported in three conventionally tilled and one no-tilled soybean trials conducted on medium and fine textured soils at four locations over two years. Trials included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 92.3% and for the tank mixture was 98.5% (n = 4) at 35–65 DAT.

The data for Axiom DF alone support a claim of barnyard grass control on medium and fine textured soils. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.5 Effectiveness against redroot pigweed (*Amaranthus retroflexus*)

Axiom DF alone
Control of redroot pigweed was reported in eight conventionally tilled field corn and eleven soybean trials conducted over four years at nine Ontario and three Quebec locations. Eight trials were conducted on coarse, seven on medium and 10 on fine textured soils at rates proposed for each. At the minimum rate proposed for each soil type, mean reported control was 84.8% (n = 19) at 22–126 DAT. Across all rates proposed for each soil type, mean reported control was 89.0% (n = 51).

Axiom DF + Aatrex Nine-0
Seven conventionally tilled field corn trials conducted at four locations over two years reported redroot pigweed control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 83.7% and for the tank mixture was 93.9% (n = 8) at 22–71 DAT.

Axiom DF + Banvel
Redroot pigweed control with Axiom DF alone and in a tank mixture with Banvel at or slightly below the requested rates for given soil textures was reported in eight conventionally tilled corn trials conducted at five locations over three years. Mean control with Axiom DF alone was 77.6% and for the tank mixture was 94.1% (n = 8) at 22–71 DAT.

Axiom DF + Marksman
Control of redroot pigweed was reported in eight conventionally tilled field corn trials conducted at five locations over three years that included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 77.6% and for the tank mixture was 99.6% (n = 8) at 22–71 DAT.

Axiom DF + Sencor 75DF
Six conventionally tilled soybean trials conducted at four locations over three years reported redroot pigweed control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a proposed rate. Mean control for Axiom DF alone was 90.0% and for the tank mixture was 94.2% (n = 6) at 23–126 DAT.

Axiom DF + Lorox DF
Redroot pigweed control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in six conventionally tilled soybean trials conducted at four locations over three years. Mean control with Axiom DF alone was 90.0% and for the tank mixture was 94.2% (n = 6) at 23–126 DAT.

Axiom DF + Sencor 75DF + Lorox DF
Control of redroot pigweed was reported in six conventionally tilled soybean trials conducted at four locations over three years that included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 90.0% and for the tank mixture was 97.5% (n = 6) at 23–126 DAT.

The data for Axiom DF alone support a claim of control of non-triazine tolerant redroot pigweed. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.6 Effectiveness against common ragweed (*Ambrosia artemisiifolia*)

Axiom DF alone
Control of common ragweed was reported in eight conventionally tilled field corn and fourteen soybean trials conducted on medium and fine textured soils over four years at one Quebec and 10 Ontario locations. Eleven trials were conducted on medium, and an additional eleven on fine textured soils at rates proposed for each. At the minimum rate proposed for each soil type, mean reported control was 81.6% (n = 19) at 22–126 DAT. Across all rates proposed for each soil type, mean reported control was 79.3% (n = 46).

Axiom DF + Aatrex Nine-0
Seven conventionally tilled field corn trials conducted on medium and fine textured soils at five locations over two years reported common ragweed control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 76.3% and for the tank mixture was 97.0% (n = 9) at 22–89 DAT.

Axiom DF + Banvel
Common ragweed control with Axiom DF alone and in a tank mixture with Banvel at or slightly below the requested rates for given soil textures was reported in nine conventionally tilled corn trials conducted on medium and fine textured soils at seven locations over three years. Mean control with Axiom DF alone was 72.1% and for the tank mixture was 91.6% (n = 9) at 22–89 DAT.

Axiom DF + Marksman
Control of common ragweed was reported in eight conventionally tilled field corn trials conducted on medium and fine textured soils at six locations over two years that included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 73.0% and for the tank mixture was 98.5% (n = 8) at 22–89 DAT.

Axiom DF + Sencor 75DF
Six conventionally tilled soybean trials conducted on medium and fine textured soils at four locations over three years reported common ragweed control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a

proposed rate. Mean control for Axiom DF alone was 76.6% and for the tank mixture was 91.5% (n = 6) at 37–126 DAT.

Axiom DF + Lorox DF
Common ragweed control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in eight conventionally tilled soybean trials conducted on medium and fine textured soils at four locations over three years. Mean control with Axiom DF alone was 76.6% and for the tank mixture was 91.5% (n = 6) at 37–126 DAT.

Axiom DF + Sencor 75DF + Lorox DF
Control of common ragweed was reported in six conventionally tilled soybean trials conducted on medium and fine textured soils at four locations over three years that included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 76.6% and for the tank mixture was 93.0% (n = 6) at 37–126 DAT.

The data for Axiom DF alone support a claim of suppression of non-triazine tolerant common ragweed on medium and fine textured soils with Axiom DF. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.7 Effectiveness against common lamb's-quarters (*Chenopodium album*)

Axiom DF alone
Control of common lamb's-quarters was reported in 21 conventionally tilled field corn and 24 soybean trials conducted over four years at 17 Ontario and six Quebec locations. Thirteen trials were conducted on coarse, 20 on medium and nine on fine textured soils at rates proposed for each. At the minimum rate proposed for each soil type, mean reported control was 78.6% (n = 32) at 16–126 DAT. Across all rates proposed for each soil type, mean reported control was 80.9% (n = 82).

Axiom DF + Aatrex Nine-0
Fifteen conventionally tilled field corn trials conducted at 11 locations over three years reported common lamb's-quarters control subsequent to Axiom DF application alone and in a tank mixture with Aatrex Nine-0 at or slightly below the proposed rate for the given soil texture. Mean control for Axiom DF alone was 78.9% and for the tank mixture was 88.0% (n = 15) at 16–89 DAT.

Axiom DF + Banvel
Common lamb's-quarters control with Axiom DF alone and in a tank mixture with Banvel at or slightly below the requested rates for given soil textures was reported in 15 conventionally tilled corn trials conducted at 11 locations over three years. Mean control with Axiom DF alone was 75.9% and for the tank mixture was 98.3% (n = 15) at 16–89 DAT.

Axiom DF + Marksman

Control of common lamb's-quarters was reported in 14 conventionally tilled field corn trials conducted at nine locations over two years that included Axiom DF alone and in a tank mixture with Marksman at the requested rate for the soil texture or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 78.9% and for the tank mixture was 99.1% (n = 14) at 16–89 DAT.

Axiom DF + Sencor 75DF

Twelve conventionally tilled soybean trials conducted at eight locations over two years reported common lamb's-quarters control subsequent to Axiom DF application alone and in a tank mixture with Sencor 75DF at or slightly below a proposed rate. Mean control for Axiom DF alone was 77.8% and for the tank mixture was 91.4% (n = 12) at 19–126 DAT.

Axiom DF + Lorox DF

Common lamb's-quarters control with Axiom DF alone and in a tank mixture with Lorox DF at requested rates and at rates of Axiom DF below those proposed for the given soil texture was reported in 12 conventionally tilled soybean trials conducted at eight locations over two years. Mean control with Axiom DF alone was 77.8% and for the tank mixture was 93.3% (n = 12) at 19–126 DAT.

Axiom DF + Sencor 75DF + Lorox DF

Control of common lamb's-quarters was reported in 12 conventionally tilled soybean trials conducted at eight locations over two years that included Axiom DF alone and in a tank mixture with Sencor 75DF + Lorox DF at a requested rate or at a rate of Axiom DF below that proposed. Average control for Axiom DF alone was 77.8% and for the tank mixture was 97.4% (n = 12) at 19–126 DAT.

The data for Axiom DF alone support a claim of suppression of non-triazine tolerant common lamb's-quarters with Axiom DF. Control was not compromised when Axiom DF was applied in conjunction with the proposed tank mixture products.

7.1.4.8 Effectiveness against weed species claimed by tank mixture products

Control of weed species claimed by the products proposed for use in tankmix combination with Axiom DF was examined to ensure that control was not adversely affected by Axiom DF inclusion. No data was provided for the tankmix products when applied alone; therefore, direct comparisons of weed control afforded by the products in the presence or absence of Axiom DF was not possible.

Corn

Control of representative weed species listed on the product labels of Aatrex Nine-0, Banvel and Marksman was reported in 24 field trials conducted over a four-year period. Eighteen trials were conducted in Ontario at 12 locations and six in Quebec at three locations. Mean reported control is summarized in Appendix III, Table 2.

The data made available demonstrate that acceptable control of weed species claimed by Aatrex Nine-0, Banvel and Marksman can be expected when the products are applied in tank mixture with Axiom DF.

Soybeans

Control of representative weed species listed on the product labels of Sencor 75DF and Lorox DF was reported in 25 field trials conducted over a three-year period. Nineteen trials were conducted in Ontario at 13 locations and six in Quebec at five locations. Mean reported control is summarized in Appendix III, Table 3.

The data made available demonstrate that acceptable control of weed species claimed by Sencor 75DF and Lorox DF can be expected when the products are applied in tank mixture with Axiom DF.

7.2 Information on the occurrence or possible occurrence of the development of resistance

To address the issue of development of herbicide resistance, the following information will be presented on the Axiom DF label:

> "For resistance management, Axiom DF is a Group 15 and Group 5 herbicide. Any weed population may contain plants naturally resistant to Axiom DF and other Group 15 and Group 5 herbicides. The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds will not be controlled by Axiom DF or other Group 15 or Group 5 herbicides.
>
> To delay herbicide resistance:
>
> Avoid the exclusive, repeated use of Axiom DF or other herbicides in the same herbicide group.
>
> Rotate with herbicides from a different herbicide group that control the same weeds as Axiom DF.
>
> Use tankmixes with herbicides from a different group when such a use is permitted.
>
> Integrate tillage or other mechanical cultural control methods into weed control programs whenever practical.
>
> Prevent movement of resistant weed seeds to other fields by cleaning harvesting and tillage equipment and planting clean seed.
>
> Keep accurate records of crop rotation and herbicides used for each of your fields.
>
> For further information contact your Bayer representative."

7.3 Effects on the yield of treated plants or plant products in terms of quantity and quality

Field corn

Axiom DF alone

A total of 12 trials conducted in the presence of weeds with the proposed rates of Axiom DF were taken to maturity and assessed for any effect on field corn yield. Mean reported yield following application of Axiom DF at the maximum proposed rate for each soil type was 181% ($n = 6$) of the untreated check. Across all rates for each soil type, yield averaged 153% ($n = 28$) of the check. No data was available for rates in excess of the maximum requested.

Axiom DF + Aatrex Nine-0

Four trials reported field corn yield following application of the maximum proposed rate of the tank mixture (Axiom DF + Aatrex Nine-0 at 0.84 + 1.5 kg a.i./ha, respectively) and Axiom DF alone at 0.84 kg a.i./ha. Mean reported yield for the tank mixture was 166% of the untreated check, while Axiom DF alone yielded 144%. No data was available for the tank mixture when applied at rates above the maximum proposed.

Axiom DF + Banvel

Field corn yield was reported in four trials in which Axiom DF was applied alone at 0.84 kg a.i./ha and in combination with Banvel at the maximum proposed tankmix rate (Axiom DF + Banvel at 0.84 + 0.6 kg a.i./ha, respectively). Mean reported yield for the tank mixture was 157% of the untreated check and for Axiom DF alone was 144%. Tankmix data at rates above the requested maximum was not available.

Axiom DF + Marksman

Four side-by-side trials reported field corn yield following application of Axiom DF alone at 0.84 kg a.i./ha and in tankmix combination with Marksman at the maximum requested rate of 1.74 kg a.i./ha. Mean reported yield was 150% for the Axiom DF + Marksman tank mixture and 144% for Axiom DF alone. No data was available for rates above the proposed maximum.

Soybean

Axiom DF alone

A total of 13 trials conducted in the presence of weeds with the proposed rates of Axiom DF were taken to maturity and assessed for any effect on field corn yield. Mean reported yield following application of Axiom DF at the maximum proposed rate on each soil type was 164% ($n = 12$) of the untreated check. Across all rates for each soil type, yield averaged 173% ($n = 25$) of the check. The mean yield of 144% across two trials was reported following application at 1.64× the maximum requested rate.

Axiom DF + Sencor 75DF

Four trials reported soybean yield following application of Axiom DF alone at 0.84 kg a.i./ha and in a tank mixture with Sencor 75DF at the maximum requested use rate (Axiom DF + Sencor 75DF at 0.84 + 0.625 kg a.i./ha, respectively). Mean reported yield for the tank mixture was 146% of the untreated check, while Axiom DF alone yielded 129%. Data was not available for the tank mixture at rates above the proposed maximum.

Axiom DF + Lorox DF

Soybean yield was reported in four trials in which Axiom DF was applied alone at 0.84 kg a.i./ha and in tankmix combination with Lorox DF at the maximum requested rate (Axiom DF + Lorox DF at 0.84 + 1.15 kg a.i./ha, respectively). Expressed as a percentage of the untreated check, mean yield for the tank mixture was 136% and for Axiom DF alone was 129%. No data was available for rates in excess of the proposed maximum.

Axiom DF + Sencor 75DF + Lorox DF

Four trials reported soybean yield following application of Axiom DF alone at 0.84 kg a.i./ha and in a tank mixture with Sencor 75DF and Lorox DF at the maximum proposed use rates (Axiom DF + Sencor 75DF + Lorox DF at 0.84 + 0.5 + 1.0 kg a.i./ha, respectively). Mean yield for the tank mixture was 145% of the untreated check, while Axiom DF alone yielded 129%. Data was not available for the tank mixture at rates above the requested maximum.

7.4 Phytotoxicity to target plants (including different varieties) or target plant products

7.4.1 Field corn

Axiom DF alone

Field corn tolerance to a pre-emergent application of Axiom DF at the maximum proposed use rate by soil texture was evaluated in 14 trials conducted over a three-year period. Two trials were conducted in Quebec at one location and 12 in Ontario at eight sites. Six corn hybrids were tested. Phytotoxicity data was reported as a visual assessment of crop injury.

Application of Axiom DF at the maximum use rate for the soil textures specified averaged 0% (n = 10) at 8–25 DAT and 1.5% (n = 10) at 31–45 DAT. No data was available for rates in excess of the proposed maximum.

The data submitted demonstrated acceptable crop safety for a pre-emergent application of Axiom DF at 0.6–1.0 kg a.i./ha to conventionally tilled field corn.

Axiom + Aatrex Nine-0

Tolerance of conventionally tilled field corn to a pre-emergent application of Axiom DF + Aatrex Nine-0 was reported in six trials conducted in Ontario across two years. Three field corn hybrids were represented. Phytotoxicity was reported as a visual assessment of crop injury.

Mean crop injury following application of Axiom DF + Aatrex Nine-0 at the proposed maximum rate of 0.84 + 1.5 kg a.i./ha was 0% (n = 5) at 10–25 DAT and 0.2% (n = 6) at 31–45 DAT. In these same trials, mean injury following application of Axiom DF alone at 0.84 kg a.i./ha was 0% (n = 5) at 10–25 DAT and 0.8% (n = 6) at 31–45 DAT.

The submitted data demonstrated acceptable crop tolerance of conventionally tilled field corn to a pre-emergent application of Axiom DF + Aatrex Nine-0 at a maximum rate of 0.84 + 1.5 kg a.i./ha.

Axiom DF + Banvel

Field corn tolerance to a pre-emergent application of Axiom DF + Banvel at the proposed maximum use rate for the specified soil texture was reported in six field trials conducted across three years with five corn hybrids. An additional three trials were conducted on coarse and medium textured soils in which Axiom DF was included at rates slightly in excess of those proposed for use (0.67 and 0.84 kg a.i./ha on coarse and medium textured soils, respectively). Phytotoxicity was reported as a visual assessment of crop injury.

Mean visual injury over all trials following application of the tank mixture was 1.3% (n = 7) at 10–25 DAT and 0.3% (n = 7) at 31–45 DAT. Seven of these trials allowed for a side-by-side comparison with Axiom DF alone at the same rate as included in the tank mixture. Mean reported injury for Axiom DF alone and in a tank mixture with Banvel was 0% and 0.4%, respectively, (n = 5) at 10–25 DAT, and 0.7% and 0.3%, respectively, (n = 7) at 31–45 DAT.

The submitted data demonstrated acceptable crop tolerance of conventionally tilled field corn to a pre-emergent application of Axiom DF + Banvel at a maximum rate of 0.84 + 0.6 kg a.i./ha.

Axiom DF + Marksman

Tolerance of conventionally tilled field corn to a pre-emergent application of Axiom DF + Marksman at the requested use rate for specified soil types was reported in six trials conducted in Ontario with five corn hybrids. An additional three trials conducted on coarse and medium soils included the tank mixture with Axiom DF inclusion at rates slightly in excess of those proposed for the soil type on which the trial was conducted (0.67 and 0.84 kg a.i./ha for coarse and medium textured soils, respectively). Phytotoxicity was reported as a visual assessment of crop injury.

Across all trials, mean visual injury following application of the tank mixture was 0.8% (n = 7) at 10–25 DAT and 0.8% (n = 6) at 31–45 DAT. Seven of these trials allowed for a side-by-side comparison with Axiom DF alone at the same rate as included in the tank mixture. Mean reported injury following application of Axiom DF alone and in a tank mixture with Marksman was 0% and 0.4%, respectively, (n = 5) at 10–25 DAT, and 0.7% and 0.4%, respectively, (n = 7) at 31–45 DAT.

The submitted data demonstrated acceptable crop tolerance of conventionally tilled field corn to a pre-emergent application of Axiom DF + Marksman at a maximum rate of 0.84 + 1.74 kg a.i./ha.

7.4.2 Soybean

Axiom DF alone

Soybean tolerance to a pre-emergent application of Axiom DF at the maximum proposed use rate by soil texture was evaluated in 19 trials conducted over a three-year period. Three trials were conducted in Quebec at three locations and 16 in Ontario at 10 sites. Fifteen soybean varieties were tested. Phytotoxicity data was reported as a visual assessment of crop injury. An additional three trials were conducted on coarse soils at rates in excess of those proposed for the soil type (0.84 kg a.i./ha).

Across all trials in which Axiom DF was applied at or slightly in excess of the maximum use rate for the soil textures specified, mean injury averaged 1.6% (n = 13) at 12–27 DAT and 0.6% (n = 15) at 28–52 DAT. Two trials conducted in 1997 reported soybean injury following Axiom DF application at 1.68 times the proposed maximum use rate. Mean reported injury was 5.0% (n = 2) at 15–23 DAT and 2.0% (n = 2) at 33–35 DAT.

The data submitted demonstrated acceptable crop safety for a pre-emergent application of Axiom DF at 0.6–1.0 kg a.i./ha to conventionally tilled soybean.

Axiom DF + Sencor 75DF

Soybean tolerance to a pre-emergent application of Axiom DF + Sencor 75DF at the proposed maximum use rate for the specified soil texture was reported in four field trials conducted across three years with three soybean varieties. An additional seven trials were conducted on coarse and medium textured soils in which Axiom DF was included at rates slightly in excess of those proposed for use (0.67 and 0.84 kg a.i./ha on coarse and medium textured soils, respectively). An additional four soybean varieties were represented. Phytotoxicity was reported as a visual assessment of crop injury.

Mean visual injury over all trials following application of the tank mixture was 4.3% (n = 6) at 13–27 DAT and 2.0% (n = 8) at 28–37 DAT. In these same trials, mean injury following application of Axiom DF alone at the same rate as included in the tank mixture was 2.8% (n = 6) at 13–27 DAT and 1.1% (n = 8) at 28–37 DAT.

The submitted data demonstrated acceptable crop tolerance of conventionally tilled soybean to a pre-emergent application of Axiom DF + Sencor 75DF at a maximum rate of 0.84 + 0.625 kg a.i./ha.

Axiom DF + Lorox DF

Tolerance of conventionally tilled soybean to a pre-emergent application of Axiom DF + Lorox DF at the requested use rate for specified soil types was reported in four trials conducted over a three-year period with three soybean varieties. An additional seven trials conducted on coarse and medium soils included the tank mixture with Axiom DF inclusion at rates slightly in excess of those proposed for the soil type on which the trial was conducted (0.67 and 0.84 kg a.i./ha for coarse and medium textured soils, respectively). Phytotoxicity was reported as a visual assessment of crop injury.

Across all trials, mean visual injury following application of the tank mixture was 2.8% (n = 6) at 13–27 DAT and 1.6% (n = 8) at 28–37 DAT. In these same trials, mean injury following application of Axiom DF alone at the same rate as included in the tank mixture was 2.8% (n = 6) at 13–27 DAT and 1.1% (n = 8) at 28–37 DAT.

The submitted data demonstrated acceptable crop tolerance of conventionally tilled soybean to a pre-emergent application of Axiom DF + Lorox DF at a maximum rate of 0.84 + 1.15 kg a.i./ha.

Axiom DF + Sencor 75DF + Lorox DF

Soybean tolerance to a pre-emergent application of Axiom DF + Sencor 75DF + Lorox DF at the proposed maximum use rate for the specified soil texture was reported in four field trials conducted across three years with three soybean varieties. An additional seven trials were conducted on coarse and medium textured soils in which Axiom DF was included at rates slightly in excess of those proposed for use (0.67 and 0.84 kg a.i./ha on coarse and medium textured soils, respectively). An additional four soybean varieties were represented. Phytotoxicity was reported as a visual assessment of crop injury.

Mean visual injury over all trials following application of the tank mixture was 3.8% (n = 6) at 13–27 DAT and 1.9% (n = 8) at 28–37 DAT. In these same trials, mean injury following application of Axiom DF alone at the same rate as included in the tank mixture was 2.8% (n = 6) at 13–27 DAT and 1.1% (n = 8) at 28–37 DAT.

The submitted data demonstrated acceptable crop tolerance of conventionally tilled soybean to a pre-emergent application of Axiom DF + Sencor 75DF + Lorox DF at a maximum rate of 0.84 + 0.5 + 1.0 kg a.i./ha.

7.5 Observation on undesirable or unintended side effects

7.5.1 Impact on succeeding crops

The claim that field corn and soybeans may be reseeded immediately should a crop failure so necessitate was supported by 11 field corn and 18 soybean trials in which the crops were seeded following a pre-plant incorporation of Axiom DF at rates equal to or in excess of the maximum proposed for each soil type. Field corn trials were conducted across two years at one Quebec and three Ontario locations. Mean reported injury was 2.0% (n = 4) at 13–27 days after planting (DAP) and 0.6% at 34–44 DAP. Average yield at the maximum application rate for the specified soil texture was 179% (n = 3) of the untreated check. Soybean trials were conducted over a three-year period at 12 Ontario and two Quebec locations. Mean reported injury was 3.7% (n = 6) at 13–25 DAP and 0.8% at 27–64 DAP. Mean yield at the maximum proposed use rate for the specific soil types examined was 143.3% (n = 6) of the untreated check.

The claim that winter wheat can be seeded four months following product application was supported by results of three trials conducted in Ontario at three locations in 1997–1998. No visual injury of winter wheat was reported when assessed at 30–37 days after seeding into soil treated previously with Axiom DF at rates of up to 1.68 kg a.i./ha

(1.68× the maximum proposed). Crop yield did not differ from that of the untreated checks.

No data was submitted to support a 12-month recropping interval for all other crops. Instead, a rationale was submitted on the basis of current knowledge of the chemical groups included in Axiom DF. The maximum rate of Axiom DF would result in the application of flufenacet (an acetanilide herbicide) at 800 g a.i./ha and metribuzin at 200 g a.i./ha. Metribuzin is registered for use in eastern Canada on several crops at rates of up to 1.125 kg a.i./ha (5.6× the maximum use in Axiom DF). Flufenacet is considered to be slightly to moderately persistent, with similar DT_{50}s to other chloroacetamide herbicides that do not have rotational cropping restrictions. It is therefore considered unlikely that recropping concerns would differ significantly between these chloroacetamides.

On the basis of the above data and information, the claim that field corn and soybeans may be reseeded immediately after application, winter wheat four months after application and any crop the following year, is acceptable.

7.6 Economics

Canadian corn and soybean production is centred in Ontario and Quebec. In terms of area under production, corn and soybean follow tame hay and rank second and third, respectively, in both provinces.

The total harvested Canadian soybean acreage for 1999 is estimated at 999 000 ha. Ontario is expected to harvest 860 000 ha and Quebec 137 000 ha. Canadian production in 1999 is forecasted to be 2 765 900 metric tonnes, with Ontario and Quebec contributing to over 99% of the national total. The trade prediction for soybean in 1999–2000 is for exports to exceed imports. Excluding oilseed products, soybean exports will likely be in the vicinity of 900 000 metric tonnes and imports approximately 400 000 metric tonnes.

The 1999 Canadian grain corn estimate is for 1 140 800 harvested ha, of which 728 000 ha is estimated to be harvested in Ontario and 366 000 ha in Quebec. Ontario and Quebec are expected to contribute approximately 97% of the total national production of 9 096 300 metric tonnes. While exports will likely remain high relative to the past five-year mean, Canada is nevertheless expected to be a small net importer of grain corn (800 000 metric tonnes exported and 900 000 metric tonnes imported) in 1999–2000.

In addition to grain corn, Canada is forecasted to harvest 6 605 200 metric tonnes of fodder corn from 186 400 ha in 1999. Eastern Canada fodder corn acreage will be greatest in Ontario at an estimated 121 400 ha, followed by Quebec at 38 000 ha, Nova Scotia at 1500 ha and New Brunswick at 1200 ha.

In 1998, farm cash receipts for eastern Canadian corn and soybean production was $622.6 million and $797.5 million, respectively.

Weed control is essential for successful field crop production. Weeds may reduce crop yields by direct competition for light, moisture and nutrients. Light infestations may reduce corn yield by 10–15%, while severe infestations can reduce yield by 50% or more. Similar levels of yield reduction may also occur for soybeans. In addition to quantitative yield reductions, weed presence may also reduce the quality of the harvested crop, delay crop dry-down, increase harvest losses and impede harvest operations.

Data made available for the pre-emergent use of Axiom DF has demonstrated that acceptable control and suppression of several annual grass and broadleaf weeds common to corn and soybean producing areas of eastern Canada can be expected when the product is used according to label directions. Axiom DF provides eastern Canadian field corn and soybean growers with another pre-emergent herbicide option for control and suppression of several common annual grass and broadleaf weeds.

7.7 Sustainability

7.7.1 Survey of alternatives

Several herbicide options are available for pre-emergent weed control in field corn and soybeans. Dimethenamid and *s*-metolachlor, like flufenacet, are chloroacetamides and primarily active on annual grasses. Products containing dimethenamid and *s*-metolachlor are registered for use on both corn and soybeans. Pre-emergent control of several annual grass and broadleaf weed species in soybeans and imazethapyr tolerant corn is also provided by products containing imazethapyr. As with Axiom DF, products containing dimethenamid, *s*-metolachlor and imazethapyr may be applied in tank mixtures with other specific herbicides registered for pre-emergent use on corn and soybeans to broaden the spectrum of weeds controlled.

7.7.2 Compatibility with current management practices including integrated pest management

As with other pre-emergent corn and soybean herbicides, use of Axiom DF does not preclude the use of other herbicides for pre-emergent or post-harvest control of weed species not controlled by the product when applied alone or with labelled tankmix products. Other herbicides may also be applied sequentially with Axiom DF should uncontrolled weed growth necessitate their application.

Cultivation and crop rotation are two principal non-chemical methods of weed control. Use of Axiom DF would not exclude pre-seeding or post-harvest tillage. Rotational cropping options are such that growers have considerable flexibility regarding the selection of the following crop.

7.7.3 Contribution to risk reduction

The amount of active ingredient applied per hectare with Axiom DF is lower than that of other chloroacetamide products.

7.8 Conclusion

The data provided indicates that, when used according to label directions, Axiom DF can be applied pre-emergent to conventionally tilled field corn and soybeans for control and suppression of specific annual grass and broadleaf weeds. Axiom DF may be tankmixed with Aatrex Nine-0, Banvel and Marksman in field corn and with Sencor 75DF, Lorox DF and Sencor 75DF + Lorox DF in soybeans for broader spectrum weed control. Applications should not be made on sand soils or on coarse soils with less than 2% OM. In the event of crop failure, field corn and soybeans may be reseeded immediately. Winter wheat may be planted four months after application and any crop the following year.

Insufficient data for review purposes was submitted to support pre-plant surface, pre-plant incorporated (corn and soybeans) and post-emergent (corn only) application timings, and use in no-tillage systems. Insufficient data was also submitted to support claims of fall panicum, large crabgrass and wild mustard control and pre-emergent use on soybeans when applied in a tank mixture with Pursuit herbicide.

7.8.1 Summary

Crops:	field corn and soybeans	
Varieties:	all field corn hybrids, consult Bayer for possible sensitive soybean varieties	
Application timing:	apply pre-emergent to the crop and weeds	
Product:	Axiom DF	
Rate of application:	coarse textured soils:	0.84–1.12 kg/ha (0.6–0.76 kg a.i./ha)
	medium textured soils:	1.12–1.26 kg/ha (0.76–0.84 kg a.i./ha)
	fine textured soils:	1.26–1.47 kg/ha (0.84–1.0 kg a.i./ha)
Weed species controlled:	green foxtail, giant foxtail, redroot pigweed (all soil textures), and yellow foxtail, barnyard grass (medium and fine soil textures only)	
Weed species suppressed:	lamb's-quarters (all soil textures), common ragweed (medium and fine textured soils only)	
Tankmix option:	field corn:	Aatrex Nine-0, Banvel, Marksman
	soybean:	Sencor 75DF, Lorox DF, Sencor 75DF + Lorox DF

8.0 Overall conclusion

Axiom DF (flufenacet + metribuzin) provides commercially acceptable crop tolerance to field corn and soybeans when applied at 0.84–1.47 kg/ha (0.6–1.0 kg a.i./ha). Axiom DF will control green foxtail, giant foxtail and redroot pigweed, and provide suppression of lamb's-quarters on coarse, medium and fine soils, and control yellow foxtail and barnyard grass, and suppress common ragweed on medium and fine soils. Axiom DF may be tankmixed with Aatrex Nine-0, Banvel and Marksman in field corn and with Sencor 75DF, Lorox DF and Sencor 75DF + Lorox DF in soybeans for broader spectrum weed control.

Metabolism studies in rats demonstrated that flufenacet was rapidly absorbed, metabolized and excreted by both sexes following oral exposure to either single or multiple doses. Tissue residues were very low, often at the limits of detection, indicating a low propensity for accumulation. The major metabolites were glutathione conjugates.

Flufenacet was of slight to moderate acute toxicity via the oral route, and of low acute toxicity via the dermal and inhalation routes. It was minimally irritating to the eye and non-irritating to the skin, and it was a dermal sensitizer. The formulation Axiom DF herbicide was moderately toxic via the oral route, of low toxicity by the dermal route, was slightly toxic by the inhalation route, was minimally irritating to the eye, was non-irritating to the skin and was a slight skin sensitizer.

Short- and long-term feeding studies revealed similar effects in mice, rats and dogs. The target organs included liver, thyroid, kidney and the hematopoeitic and nervous systems (including the eye). Mechanistic data indicated that the effects observed in rats on thyroid hormone levels and thyroid gland histopathology were the result of increased T_4 clearance by the liver. The thyroid effects were also observed in the dog and the physiological response of the dog to these changes in thyroid hormone homeostasis more accurately reflects the potential human response. Anemia was observed in rats and mice. Methemoglobinemia appears to be the cause of the eye effects, and oxidative stress in general the source of the neurotoxicity. There was no evidence that flufenacet is mutagenic or carcinogenic. The young did not demonstrate an increased sensitivity to flufenacet exposure, and there was no evidence of teratogenicity.

The metabolic fate of flufenacet in plants grown in soil treated with (fluorophenyl- or thiadiazole-labelled) flufenacet was studied in corn and soybeans. The metabolic profile of flufenacet in plants indicated that flufenacet was cleaved to yield an acetamide and thiadone moiety. The fluorophenyl acetamide portion was directly conjugated with glutathione and further metabolized, yielding flufenacet cysteine conjugates. The thiadone moiety formed various conjugates, the most important being the corresponding *N*-glucoside. Flufenacet oxalate was identified as a major plant metabolite in corn, and the malonylalanine conjugate was predominant in soybeans. The parent compound was not detected in any of the two labels. On the basis of the plant metabolism studies, the ROC was defined as flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

Animal metabolism studies were conducted in goats and hens by administering flufenacet (fluorophenyl- or thiadiazole-labelled) flufenacet. Flufenacet (thiadiazole label) was rapidly cleaved to yield thiadone as the major metabolite, which was primarily conjugated to glucuronic acid. Flufenacet (fluorophenyl label) conjugated with glutathione with further biodegradation to the mercapturic acid pathway, with additional formation of cysteine or mercapturic acid conjugates. The goat and hen metabolism studies suggested that flufenacet was extensively metabolized in the body with negligible residues of the detected in meat, milk or eggs. On the basis of the similarity of the goat, laying hen and rat metabolic profiles, the ROC was defined as flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

Conclusions drawn from the environmental fate studies corraborates with the animal and plant metabolism conclusions. There were no novel soil metabolites of flufenacet detected in the soil dissipation studies. The only metabolites detected were five metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety.

In the confined rotational crop studies, kale (leaves), turnips (tops and roots) and wheat (grain and straw) were planted as secondary crops at 33, 157 and 361 days, respectively, after a single soil application of radiolabelled flufenacet at 1.6×. All crops were harvested at maturity. Analysis of soil cores, at application and planting, demonstrated that the soil TRRs decreased by approximately half the levels (44%; 0.26 ppm) after 153 days. No parent compound was detected in the rotational crops. In the event of crop failure, corn or soybean may be replanted immediately in or on treated soil. Winter wheat may be planted four months after an application of flufenacet (Axiom DF). The residue data corroborated the proposed rotational crop plant-back interval of four months for winter wheat. The confined crop rotation study supported the ROC, flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety, as defined from the plant and animal metabolism studies.

A common moiety method was used for the analysis of flufenacet equivalent residues in plant and animal commodities. The analytical method involved the conversion of the parent flufenacet and its metabolites through oxidation and subsequent hydrolysis to a common analyte, 4-fluoro-*N*-methylethyl benzeneamine. Residues of 4-fluoro-*N*-methylethyl benzeneamine were removed from matrices by steam distillation followed by derivatization to the 4-fluoro-*N*-methylethyl benzeneamine trifluoroacetamide for quantification by GC–MSD. The LOQ was 0.1 ppm for forage, fodder and hay and 0.05 ppm for seeds and grain. The LOQ was 0.01 ppm for milk and 0.05 ppm for meat and meat by-products. The validation of the analytical method was performed by extracting flufenacet-derived residues from the aged radioactive plant and animal matrices collected from the metabolism studies. The validation supported the repeatability and reproducibility of the analytical method for the determination of flufenacet equivalent residues in plant and livestock matrices.

Supervised residue trials studies were conducted in or on corn and soybean RACs treated with flufenacet with a single pre-plant or pre-emergent broadcast application at a rate of 1 kg a.i./ha. Residues of flufenacet equivalent detected in corn grain were less than 0.05 ppm (LOQ) and less than 0.1 ppm in soybean seed. Corn and soybean processing

studies indicated the levels of flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety were less than the LOQ in all corn and soybean matrices. Flufenacet equivalent residues, therefore, did not concentrate in any of the corn or soybean processed commodities that simulated commercial processing practices.

Residues of flufenacet and its major metabolites were stable at –24°C in corn and soybean matrices for at least 11 months. Plant metabolism and residue samples were analyzed within this time frame. Residues of flufenacet equivalents were stable up to 30 months in goat and poultry tissues, eggs and milk. Residues of flufenacet oxalate were stable in goat tissues and milk for approximately 18 months. Animal metabolism and residue samples were analyzed within respective time frames.

A livestock feeding study with flufenacet was not conducted, since no residues of the parent compound above the LOQ were detected in feed commodities from the treated crops. Since flufenacet oxalate was a novel plant metabolite, however, cows were administered highly exaggerated doses of flufenacet oxalate equivalent to 14–148× in their feed. At the maximum anticipated dietary burden of 0.5 ppm, no residues of flufenacet or flufenacet oxalate were expected in the meat or the milk of the cattle that had been fed with feed commodities of the crops grown in flufenacet-treated soil. A poultry feeding study was not conducted, on the basis of the results of the hen metabolism study and crop field trials. Residues transferred to poultry tissues and eggs from the feeding of the commodities grown in soil treated with flufenacet at GAP were also expected to be less than 0.001 ppm. Flufenacet oxalate was rapidly excreted and only small amounts were detected in tissues and eggs. Also, no residues of the parent compound were detected in any of the matrices in the plant metabolism studies.

It is proposed that MRLs of 0.05 and 0.1 ppm in field corn grain and soybean seed, respectively, be promulgated in the Division 15, Table II of the *Food and Drugs Act* and Regulations. Also, MRLs of 0.01 ppm for milk and 0.05 ppm for meat, meat by-products and eggs should be promulgated to cover the potential transfer of residues of flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzeneamine moiety in milk, eggs, meat and meat by-products of cattle and poultry as a result of feeding treated crop parts to livestock. The proposed MRLs for the Canadian use of flufenacet in or on field corn grain and soybean seed are the same as the U.S. tolerances.

A chronic dietary risk assessment indicated that the PDI is 30% of the ADI for all population subgroups. The proposed Canadian use of flufenacet in or on field corn and soybean, therefore, will not pose an unacceptable dietary (both food and water) risk to any segment of the Canadian population, including infants, children and adults.

A short-term dermal toxicology study was deemed most relevant for the risk assessment for both farmers and custom applicators. The MOEs are acceptable for all mix, load and application activities associated with the use of Axiom DF Herbicide, provided that workers wear two layers of clothing.

Flufenacet is stable to hydrolysis and photolysis in soil and water. It is slightly to moderately persistent in soils under field conditions. It is, however, persistent in aerobic and anaerobic aquatic systems. The laboratory adsorption and leaching studies indicated that flufenacet is mobile and has a leaching potential in coarse textured soils.

Flufenacet is toxic to fish, aquatic plants and non-target terrestrial plants. The proposed use pattern has a potential to significantly affect the aquatic and terrestrial habitat because of spray drift and runoff. To protect aquatic habitat, a buffer zone of 40 m is required between the last spray swath and the edge of the sensitive areas such as wetlands, ponds, lakes and rivers. A buffer zone of 24 m is required between the downwind edge of the boom and terrestrial habitats, including forested areas, shelter belts, woodlots, hedgerows and shrublands.

Label amendments:

> "For Use in Eastern Canada Only"
>
> "Wear long-sleeve shirt, long pants, coveralls and chemical-resistant gloves when mixing, loading and applying and during clean-up and repair activities."
>
> "This product is toxic to fish, aquatic plants and non-target terrestrial plants. Overspray or drift to sensitive habitats should be avoided. A buffer zone of 24 metres is required between the downwind edge of the boom and sensitive terrestrial habitats including forested areas, shelter belts, woodlots, hedgerows, and shrublands. A buffer zone of 40 metres is required between the downwind edge of the boom and sensitive aquatic habitats including sloughs, ponds, prairie potholes, lakes, rivers, streams, and wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment and containers or disposal of waste."
>
> "Do not apply during periods of dead calm, when winds are gusty or when wind speed is greater than 15 km/h at 2 metres high above ground at the site of application."
>
> "When a tank mixture is used, consult the label of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture."

Reference to use on no-till soybeans and field corn has been removed from the label.

Reference to preplant surface, preplant incorporated and post-emergent application timings has been removed from the label.

Reference to use in a tank mixture with Pursuit Herbicide has been removed from the label.

A claim of fall panicum, large crabgrass and wild mustard control has been removed from the label.

9.0 Toxic substance management policy

During the review of FOE 5043 (flufenacet) Technical and AXIOM® DF, the PMRA has considered the implications of the federal Toxic Substances Management Policy (TSMP) and the PMRA Regulatory Directive DIR99-03 -*The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy* and has concluded the following:

- Flufenacet is persistent in aerobic water systems, with a half-life of 458 days, which exceeds the Track-1 cut-off criterion for water (≥182 days). The half-life in soil (67 days) is below the TSMP Track-1 cut-off criterion (≥182 days). Although a half-life in air was not submitted, flufenacet is non-volatile from moist soil and water surfaces, based on values for vapour pressure and Henry's Law Constant.

- Flufenacet will not bioaccumulate. Studies have shown that the Bioconcentration Factor (BCF) is 165 for whole fish, which is below the TSMP Track-1 cut-off criterion of BCF (≥5000). The log of the octanol-water partition coefficient (log K_{ow}) is 3.2, which is below the TSMP Track-1 cut-off criterion of ≥5.0.

- With respect to human and animal health, flufenacet does not meet TSMP Track-1 criteria for toxicity (see Chapters 3 and 4 of this document). The eco-toxicity of flufenacet is described in Chapter 6.

- Flufenacet forms persistent major transformation products (14-23% of applied). Values for the log K_{ow} and transformation half-lives of these products were not reported. These transformation products are acids and, therefore, are more polar than the parent compound, which is an ester. Further, they are more soluble in water and less soluble in octanol, and it is expected that their log K_{ow} will be lower than the parent and also below the TSMP Track-1 cut-off criterion. Acids, however, are usually more stable than the ester with respect to hydrolysis. The log K_{ow} studies with the persistent major transformation products (FOE sulfonic acid and FOE oxalate)are required to confirm the predictions based on chemistry.

- The technical grade of flufenacet does not contain any by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concerns are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.

The formulated product does not contain any formulants that are known to be TSMP Track-1 substances.

10.0 Regulatory Decision

FOE 5043 Technical (flufenacet) and Axiom DF herbicide have been granted temporary registrations for use as pre-emergent control of specific annual grass and broadleaf weeds in field corn and soybeans, pursuant to Section 17 of the Pest Control Product Regulations, subject to the generation of the following study:

developmental neurotoxicity study

List of abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ARfD	acute reference dose
AST	aspartate aminotransferase
bw	body weight
CAS	Chemical Abstracts Service
d	day
DAP	days after planting
DAT	days after treatment
DEEM	Dietary Exposure Evaluation Model
DNA	deoxyribonucleic acid
DT_{50}	dissipation time (50%)
EC_{25}	effect concentration (25%)
EC_{50}	effect concentration (50%)
EEC	expected environmental concentration
F_0	parental animals
F_1	first generation offspring
F_2	second generation offspring
FOB	functional observational battery
FT_4	free thyroxine
GAP	good agricultural practices
GC	gas chromatography
h	hour
Hb	hemoglobin
Hct	hematocrit
HPLC	high performance liquid chromatography
K_d	Freundlich adsorption coefficient (ratio of concentration in the soil phase to that in the aqueous phase, under test conditions)
K_{oc}	organic carbon adsorption coefficient (relates K_d to the organic carbon content of the soil sample)
K_{ow}	octanol–water partition coefficient
LC_{50}	lethal concentration (50%)
LD_{50}	lethal dose (50%)
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
LOQ	limit of quantitation
MOE	margin of exposure
MRL	maximum residue limit
MSD	mass selective detection
n	number of trials
nm	nanometers
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

NZW	New Zealand White
OM	organic matter
Pa	pascal
PDI	potential daily intake
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
ppm	parts per million
RAC	raw agricultural product
RBC	red blood cells
ROC	residue of concern
RP	reverse phase
SD	Sprague–Dawley
SF	safety factor
T_3	tri-iodothyronine
T_4	thyroxine
TRR	total radioactive residue

Appendix I Summary of the toxicity studies with flufenacet

Metabolism

Metabolism studies in rats demonstrated that FOE 5043 (flufenacet) was rapidly absorbed, metabolized and excreted by both sexes following oral exposure to either single or multiple doses. In the [fluorophenyl-UL-^{14}C]-labelled flufenacet experiments, the recovered radioactivity ranged from 60 to 75%, and at least 91% of the administered radiolabel was recovered in the experiments with [thiadiazole-2-^{14}C]-labelled flufenacet within 72 h post-dose. The urine was the major route of excretion following all dosing regimens, and for the [fluorophenyl-UL-^{14}C]-labelled flufenacet, smaller amounts of radiolabel were eliminated as CO_2 and CH_4. No volatile radiolabelled compounds were detected after dosing with [thiadiazole-2-^{14}C]-labelled flufenacet, indicating that the phenyl ring was not cleaved. The analysis of the plasma curves indicated that after dosing with [fluorophenyl-UL-^{14}C]- and [thiadiazole-2-^{14}C]-labelled flufenacet only, the fluorophenyl portion of the molecule was subjected to enterohepatic circulation. Tissue residues were very low, often at the limits of detection, indicating a low propensity for accumulation.

The major metabolites identified in the [fluorophenyl-UL-^{14}C]-labelled flufenacet experiments contained only the "fluorophenyl" moiety of the compound. The thiadiazole ring was cleaved before further metabolism. This was confirmed in the experiment using [thiadiazole-2-^{14}C]-labelled flufenacet in which the major metabolites identified were the glucuronic acid conjugate of thiadone, the oxalylacetic acid conjugate of thiadone and free thiadone. The major metabolic pathway for [fluorophenyl-UL-^{14}C]-labelled flufenacet in rats appeared to be conjugation with glutathione. Although the glutathione conjugate itself was not detected, the presence of a variety of glutathione-derived metabolites (all metabolites identified were glutathione related compounds, but the major metabolite was the N-acetylcysteine conjugate of fluorophenylacetanilide) provided sufficient circumstantial evidence for a glutathione pathway.

Study	Species and strain and doses	NOEL or NOAEL and LOEL (mg/kg bw/day)	Target organ and significant effects and comments
Acute studies			
Oral	Mice (CD-1) males and females	LD_{50} = 1331 mg/kg bw (males) and 1756 mg/kg bw (females) Study 1331 mg/kg bw	Slightly toxic
Oral	Rats (SD) males and females	LD_{50} = 1617 mg/kg bw (males) and 589 mg/kg bw (females) Study 589 mg/kg bw	Moderately toxic
Oral	Rats (SD) males	LD_{50} = 683 mg/kg bw (males)	Moderately toxic
Dermal	Rats males and females	LD_{50} > 2.0 g/kg bw (males and females)	Low toxicity
Inhalation	Rats males and females	LC_{50} > 3.74 mg/L (males and females)	Low toxicity
Skin irritation	Rabbits (NZW) males	Negative	Not a skin irritant
Eye irritation	Rabbits (NZW) males	Maximum average score = 6.16/110 at 1 h	Minimally irritating to the eyes
Skin sensitization (Buehler method)	Guinea pigs (Hartley) males	Negative	Not a skin sensitizer

Study	Species and strain and doses	NOEL or NOAEL and LOEL (mg/kg bw/day)	Target organ and significant effects and comments
Skin sensitization (maximization test)	Guinea pigs (Hartley) males	Positive	Skin sensitizer
Short term			
Dermal	Rats (CD [SD] BR) males and females 0, 20, 150 and 1000 mg/kg bw/day	NOEL = 20 mg/kg bw/day	Reversible clinical chemistry effects (decreased T_4 and FT_4) levels in both sexes and reversible histopathological liver findings in the females
90-day (d) dietary	Mice (CD-1 ICR/BR) 0, 100, 400, 1600 and 4000 ppm (0, 18.2, 64.2, 275 and 824 mg/kg bw/day males and 0, 24.5, 91.3, 432 and 1134 mg/kg bw/day females)	NOEL = 100 ppm 18.2 mg/kg bw/day (males) 24.5 mg/kg bw/day (females)	≥400 ppm: increased colloid incidence (thyroid) (males); heptocytomegaly (females and males); splenic hematopoiesis (males) and splenic pigmentation (females) ≥1600 ppm: decreased T_4 (males); increased liver weight and ratio (to body weight) (males and females); increased liver cell (individual) necrosis (males); splenic hematopoiesis (females); clinical observations such as circling, increased activity and swaying movements of the head and increased incidence of food spillage (males and females) 4000 ppm: decreased mean body weight and mean body weight gain (males and females); decreased RBC, Hb, Hct and T_3, increased platelets (males and females); decreased ovary weight and ratio (females); increased spleen weight and ratio (males); decreased kidney weight (males); increased relative kidney weight (females); increased liver weight and relative liver weights (males and females); increased ALP (males); increased AST and ALP (females)
90-d dietary	Rats (CDF F 344/BR) 0, 100, 400, 1600 and 3000 ppm males: 0, 6.0, 24.3,109.1 and 191.2 mg/kg bw/day females: 0, 7.2, 28.8, 127.2 and 224.5 mg/kg bw/day	NOAEL = 100 ppm (6.0 mg/kg bw/day)	≥400 ppm: anemia, decreased T_4, hyperplasia of kidney pelvis, liver hypertrophy, splenic hemosiderosis ≥1600 ppm: increased liver weight (males) 3000 ppm: increased spleen and thyroid weights (males)

Study	Species and strain and doses	NOEL or NOAEL and LOEL (mg/kg bw/day)	Target organ and significant effects and comments
90-d dietary	Dogs (beagle) 0, 50, 200, 800 and 2400 ppm males 0, 1.67, 7.2, 27.21 and 96.91 mg/kg bw/day females 0, 1.70, 6.9, 28.00 and 93.23 mg/kg bw/day	NOAEL = 50 ppm (1.67 mg/kg bw/day) LOAEL = 200 ppm (6.9 mg/kg bw/day)	≥200 ppm: decreased T_4, glucose and albumen, increased globulin
52-week dietary	Dogs (beagle) 0, 40, 800 and 1600 ppm males: 0, 1.29, 27.75 and 62.24 mg/kg bw/day females: 0, 1.14, 26.82 and 58.78 mg/kg bw/day	LOAEL = 1.14 mg/kg bw/day	≥40 ppm: decreased body weight gain and T_4; increased ALP, kidney epithelial hyperplasia and methemoglobin ≥800 ppm: increased liver weight and ALP, decreased AST, increased kidney epithelial hyperplasia (females); increased kidney weight, (males and females); heart weight increased, axonal degeneration and central nervous system (males and females); vacuolation of the ciliary body epithelium in eyes (males and females) 1600 ppm: hepatomegaly, decreased T_4 and T_3, increased thyroid weight (absolute and relative) (males and females); increased hypertrophy of the thyroid follicular cells (males); axonal degeneration in the sciatic nerve (males and females)
Chronic toxicity and oncogenicity			
20-month dietary	Mice (CD1-ICR/BR) 0, 50, 200 and 400 ppm males: 0, 7.4, 30.4 and 62.2 mg/kg bw/day females: 0, 9.4, 38.4 and 77.2 mg/kg bw/day	Chronic toxicity NOEL = 7.4 mg/kg bw/day (males) 9.5 mg/kg bw/day (females) Oncological NOEL = 62.2 mg/kg bw/day (males) 77.2 mg/kg bw/day (females)	Chronic: increased severity and incidence of cataracts No carcinogenic effect at the high dose
24-month dietary	Rats (CDF F 344/BR) 0, 125, 400 and 800 ppm males: 0, 1.2, 19.3 and 39.0 mg/kg bw/day females: 0, 1.5, 38.4 and 48.8 mg/kg bw/day	Chronic toxicity LOEL = 1.2 mg/kg bw/day (males) 1.5 mg/kg bw/day (females) Oncological NOEL = 39.0 mg/kg bw/day (males) 48.8 mg/kg bw/day (females)	Increased scleral mineralization, kidney epithelial hyperplasia, renal pelvis mineralization, vascular mineralization, marginal increased cataracts No carcinogenic effect at high dose

Study	Species and strain and doses	NOEL or NOAEL and LOEL (mg/kg bw/day)	Target organ and significant effects and comments
Reproduction and developmental toxicity			
Multigeneration	Rats (SD Crl: CD/BR) 0, 20, 100 and 500 ppm premating (mean P and F_1) males: 0, 1.4, 7.4 and 37.4 mg/kg bw/day females: 0, 1.5, 8.2 and 41.1 mg/kg bw/day	Maternal NOEL = 20 ppm (1.4 mg/kg bw/day) Reproductive NOEL = 100 ppm (7.4 mg/kg bw/day)	Decreased premating body weight gain, increased liver weight and liver to body weight ratio, hepatocytomegaly, increased stillbirths and pup deaths in early lactation in F_2 pups
Teratogenicity	Rats (SD Crl: CD/BR) 0, 5, 25 and 125 mg/kg bw/day	Maternal NOEL = 25 mg/kg bw/day Developmental NOEL = 25 mg/kg bw/day Teratological NOEL = 125 mg/kg bw/day	Decreased body weight, decreased body weight gain at higher doses, marginal decreased fetal body weight, delayed development (mainly delayed ossification), increased incidence of extra ribs No teratogenic effects at high dose
Teratogenicity	Rabbits (NZW) 0, 5, 25, 125 and 200 mg/kg bw/day	Maternal NOEL = 5 mg/kg bw/day Teratological NOEL = 200 mg/kg bw/day Developmental NOEL = 25 mg/kg bw/day	Liver histopathology (hypertrophy, vacuolar changes in cytoplasm) No teratogenic effects at high dose At mid and high dose skeletal variation and at high dose delayed development (mainly delayed ossification) and increased incidence of extra ribs
Mutagenicity			
Salmonella (Ames test)	*Salmonella typhimurium* TA 98, TA 100, TA 1535 and TA 1537 15–5000 μg/plate	Negative	Precipitation seen at 5000 μg/plate
Mammalian chromosomal aberration (in vitro)	Chinese hamster ovary cells 8, 40 or 200 μg/mL	Negative	
Micronucleus assay (in vivo)	CD-1 mice males and females 250 mg/kg (sacrifice at 16, 24 and 72 h)	Negative	
UDS in vitro	Primary rat hepatocytes 2.5, 5.0, 10.0, 20.0, 40.0, 60.0 and 80.0 μg/mL	Negative	Cytotoxic at doses ≥60 μg/mL
Mammalian cytogenetics (in vitro)	Chinese hamsters V79 7.8–500 μg/mL	Negative	

Study	Species and strain and doses	NOEL or NOAEL and LOEL (mg/kg bw/day)	Target organ and significant effects and comments
Special studies			
Acute neurotoxicity	Rats (Fischer 344BR) males:0, 75, 200 and 450 mg/kg bw/day females: 0, 75, 150 and 300 mg/kg bw/day	NOAEL = 75 mg/kg bw/day (systemic and neurotoxicity)	≥150/200: decreased body temperature (males and females) decreased locomotor activity (males and females), decreased 300/450 deaths(both sexes) and gait disturbances (females)
90-d dietary neurotoxicity	Rats (CDF F 344/BR) 0, 120, 600 and 3000 ppm males: 0, 7.3, 38.1 and 219 mg/kg bw/day females: 0, 8.4, 42.6 and 247 mg/kg bw/day	NOEL = 120 ppm (neurotoxicity) 7.3 mg/kg bw/day (males) 8.4 mg/kg bw/day (females)	Microscopic lesions detected at 600 and 3000 ppm (axonal swelling cerebellum and spinal cord)

Appendix II Summary of environmental effects of flufenacet to terrestrial and aquatic organisms: toxicity and margin of safety

Organisms and study type	Results and interpretation	Margin of safety[1] and comments
Earthworms (*Eisenia foetida*) Soil contact	14-d LC_{50} > 226 mg a.i./kg soil 14-d NOEC < 10 mg a.i./kg soil	27.8 No potential risk
Honey bees (*Apis mellifera*) Acute contact	48-h LD_{50} > 25 μg a.i./bee 48-h NOEC = 25 μg a.i./bee (on the basis of mortality and sublethal effect) Relatively non-toxic	No potential risk
Bobwhite quail (*Colinus virginianus*) Acute oral	LD_{50} = 1608 mg a.i./kg bw NOEC = 125 mg a.i./kg bw Slightly toxic	No potential acute oral effect
Bobwhite quail (*C. virginianus*) Acute dietary	LC_{50} > 5317 mg a.i./kg dw of diet NOEC = mg a.i./kg dw of diet Practically non-toxic	13.3 No potential acute dietary risk
Mallard (*Anas platyrhynchos*) Acute oral	LD_{50} > 2000 mg a.i./kg bw NOEC = mg a.i./kg bw Practically non-toxic	No potential acute oral effect
Mallard (*A. platyrhynchos*) Acute dietary	LC_{50} =4970 mg a.i.//kg dw of diet NOEC = mg a.i./kg dw of diet Practically non-toxic	6.1 No potential acute dietary risk
Bobwhite quail (*C. virginianus*) Reproduction	NOEC = 441 mg a.i./kg dw of diet (on the basis of hatchling weight)	4.6 No potential chronic (reproductive) risk
Mallard (*A. platyrhynchos*) Reproduction	NOEC = 88 mg a.i./kg dw of feed (on the basis of the 14-day-old survivor weight)	3.3 No potential chronic (reproductive) risk
Mouse Acute oral	LD_{50} = 1331 mg a.i./kg bw Slightly toxic	No potential acute risk
Rat Acute oral	LD_{50} = 549 mg a.i./kg bw Moderately toxic	No potential acute risk
Mouse 90-d dietary toxicity	NOEC = 100 mg a.i./kg dw of diet	90 days of continuous intake needed for potential risk
Rat 90-d dietary toxicity	NOEAL = 100 mg a.i./kg dw of diet	90 days of continuous intake needed for potential risk
Tomato Vegetative vigour test	EC_{25} = 26 g a.i./ha (on the basis of dry weight)	0.03 Potential risk
Sorghum Vegetative vigour test	EC_{25} = 7.9 g a.i./ha (on the basis of dry weight)	0.01 Potential risk

Organisms and study type	Results and interpretation	Margin of safety[1] and comments
Freshwater flea (*Daphnia magna*) Acute toxicity	48-h effect concentration (50%) (EC_{50}) = 30.9 mg a.i./L 48-h NOEC = 17.7 mg a.i./L (on the basis of the sublethal effects) Slightly toxic	65.6 No potential risk
Freshwater flea (*D. magna*) Reproductive toxicity	NOEC = 6.33 mg a.i./L (for the most sensitive end point)	23.4 No potential risk
Hyalella azteca Acute toxicity	96-h LC_{50} = 2.8 mg a.i./L Moderately toxic	1.04[2] No potential risk
Mysids (*Mysidopsis bahia*) Acute toxicity	72-h LC_{50} = 3.37 mg a.i./L NOEC =0.81 mg a.i./L (on the basis of loss equilibrium) Moderately toxic	3.0 No potential risk
Rainbow trout (*Onchorynchus mykiss*) Acute toxicity	96-h LC_{50} = 3.5 mg a.i./L 96-h NOEC = 0.41 mg a.i./L (on the basis of sublethal effects) Moderately toxic	1.51 No potential risk
Bluegill sunfish (*Lepomis macrochirus*) Acute toxicity	96-h LC_{50} = 2.3 mg a.i./L 96-h NOEC = 0.91 mg a.i./L (on the basis of sublethal effects) Moderately toxic	3.4 No potential risk
Sheepshead minnow (*Cyprinodon variegatus*) Acute toxicity	96-h LC_{50} = 3.38 mg a.i./L 96-h NOEC = 1.18 mg a.i./L (on the basis of mortality) Moderately toxic	4.4 No potential risk
Rainbow trout (*Onchorynchus mykiss*) Early life cycle toxicity	NOEC = 0.179 mg a.i./L (on the basis of swim up and growth in length)	0.67 Potential risk
Freshwater diatom (*Navicula pelliculosa*) Growth rate inhibition	EC_{50} = 3.8 mg a.i./L NOEC = 1.12 mg a.i./L (on the basis of growth)	4.1 No potential risk
Blue-green algae (*Anabaena flos-aquae*) Growth rate inhibition	120 h EC_{50} = 34.0 mg a.i./L NOEC = 3.77 mg a.i./L (on the basis of growth)	14.0 No potential risk
Green algae (*Selenastrum capricornutum*) Growth rate inhibition	$EC_{50} = 2.9 \times 10^{-3}$ mg a.i./L NOEC = 2.08×10^{-3} mg a.i./L (on the basis of growth)	0.008 Potential risk
Marine diatom (*Skeletonema costatum*) Growth rate inhibition	$EC_{50} = 5.59 \times 10^{-3}$ mg a.i./L NOEC = 3.57×10^{-3} mg a.i./L (on the basis of growth)	0.013 Potential risk
Duckweed (*Lemna gibba*) Acute toxicity	14-d $EC_{50} = 2.45 \times 10^{-3}$ mg a.i./L NOEC = 4.4×10^{-4} mg a.i./L (number of fronds)	0.002 Potential risk

1 Margin of safety = NOEC/EEC

2 0.1 LC_{50}/EEC

Appendix III Efficacy

Table 1 Rate structure of Axiom DF and accepted tank mixtures

Product or tank mixture	Application rate (kg a.i./ha)		
	Coarse soils (excluding sands and soils with less than 2% organic matter)	Medium soils	Fine soils
Axiom DF	0.6–0.76	0.76–0.84	0.84–1.0
Axiom DF + Aatrex Nine-0	0.6 + 1.0	0.76 + 1.25	0.84 + 1.5
Axiom DF + Banvel	0.6 + 0.6	0.76 + 0.6	0.84 + 0.6
Axiom DF + Marksman	0.6 + 1.43	0.76 + 1.59	0.84 + 1.73
Axiom DF + Sencor 75DF	0.6 + 0.375	0.76 + 0.5	0.84 + 0.625
Axiom + Lorox DF	0.6 + 0.85	0.76 + 1.0	0.84 + 1.15
Axiom DF + Sencor 75DF + Lorox DF	0.6 + 0.375 + 0.7	0.76 + 0.44 + 0.85	0.84 + 0.5 + 1.0

Table 2 Mean reported control of weed species listed on the Aatrex Nine-0, Banvel and Marksman labels

Weed species	Mean reported weed control		
	Axiom DF + Aatrex Nine-0	Axiom DF + Banvel	Axiom DF + Marksman
lamb's-quarters (*Chenopodium album*)	89.9% (n = 17)	92.9% (n = 21)	98.8% (n = 21)
common ragweed (*Ambrosia artemisiifolia*)	96.4% (n = 11)	93.5% (n = 12)	98.5% (n = 12)
redroot pigweed (*Amaranthus retroflexus*)	94.6% (n = 8)	95.6% (n = 11)	99.6% (n = 11)
lady's thumb (*Polygonum persicaria*)	97.2% (n = 5)	94.6% (n = 5)	98.8% (n = 5)
velvetleaf (*Abutilon theophrasti*)	n/a	93.5% (n = 4)	96.0% (n = 4)
green smartweed (*Polygonum scabrum*)	100% (n = 2)	98.5% (n = 2)	100% (n = 2)
wild mustard (*Sinapis arvensis*)	99.5% (n = 2)	94.0% (n = 2)	99.5% (n = 2)
wild buckwheat (*Polygonum convolvulus*)	96.0% (n = 2)	85.5% (n = 2)	96.5% (n = 2)

n = number of observations

Table 3 Mean reported control of weed species listed on the Sencor 75DF and Lorox DF labels

Weed species	Mean reported weed control		
	Axiom DF + Sencor 75DF	Axiom DF + Lorox DF	Axiom DF + Sencor 75DF + Lorox DF
lamb's-quarters (*Chenopodium album*)	92.3% (n = 20)	95.0% (n = 19)	96.2% (n = 19)
common ragweed (*Ambrosia artemisiifolia*)	85.5% (n = 13)	86.0% (n = 13)	91.2% (n = 13)
redroot pigweed (*Amaranthus retroflexus*)	95.9% (n = 11)	95.9% (n = 10)	97.6% (n = 10)
velvetleaf (*Abutilon theophrasti*)	97.3% (n = 6)	98.0% (n = 5)	98.2% (n = 5)
fall panicum (*Panicum dichotomiflorum*)	86.3% (n = 6)	n/a	89.7% (n = 6)
lady's thumb (*Polygonum persicaria*)	80.8% (n = 4)	n/a	89.7% (n = 3)
cocklebur (*Xanthium strumarium*)	87.0% (n = 3)	n/a	90.7% (n = 3)
witchgrass (*Panicum capillare*)	99.0% (n = 2)	99.0% (n = 2)	99.5% (n = 2)
smooth crabgrass (*Digitaria ischaemum*)	98.5% (n = 2)	98.5% (n = 2)	98.5% (n = 2)
wormseed mustard (*Erysimum cheiranthoides*)	n/a	99.5% (n = 2)	100% (n = 2)
shepherd's purse (*Capsella bursa-pastoris*)	100% (n = 1)	100% (n = 1)	100% (n = 1)
green smartweed (*Polygonum scabrum*)	100% (n = 1)	99.0% (n = 1)	100% (n = 1)
large crabgrass (*Digitaria sanguinalis*)	99.0% (n = 1)	100% (n = 1)	100% (n = 1)
wild mustard (*Sinapis arvensis*)	99.0% (n = 1)	n/a	99.0% (n = 1)
wild buckwheat (*Polygonum convolvulus*)	n/a	95.0% (n = 1)	93.0% (n = 1)
stinkweed (*Thlaspi arvense*)	n/a	96.0% (n = 1)	100% (n = 1)
annual sowthistle (*Sonchus oleraceus*)	n/a	99.0% (n = 1)	100% (n = 1)

n = number of observations